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ARCHIVES OF SURGERY

VOLUME 24 MAY, 1932 NUMBER 5

SODIUM AMYTAL

ANALYSIS OF INTRAVENOUS USE IN ONE HUNDRED AND SEVENTY-TWO SURGICAL OPERATIONS *

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Sodium amytal is the sodium salt of iso-amyl-ethyl barbituric acid. Barbituric acid derivatives have been used for years by pharmacologists and physiologists as hypnotics and occasionally as anesthetics. Fredet and Perlis were the first to succeed in inducing general anesthesia in man with compounds of this series. The preparation of sodium amytal in pure form, and in a sterile ampule together with a companion ampule of sterile distilled water sufficient to make a 10 per cent solution, enabled investigators to use in man a barbiturate producing general anesthesia by the intravenous route, that had been used successfully for several years in animal experimentation. In February, 1929, Zerfas and MacCallum published the first report of such a study.

Our interest in sodium amytal was aroused by the possibility of:

(1) Inducing a general anesthesia by a more direct method than with the inhalation anesthetics in which the lungs bear the brunt of the administration.

(2) Greater ease of administration and more pleasant, when compared to the gases, as far as the patient is concerned.

(3) The few hours of postoperative oblivion that carries the patient over an exceedingly trying period.

(4) The production of a better general anesthetic than we are accustomed to obtain with nitrous oxide and oxygen, even if combined with the latter, and producing a "balanced anesthesia," in which the burden of anesthesia is placed partly on the preliminary medication and partly on the general anesthetic.

* Submitted for publication, July 18, 1931.

* From the Department of Surgery, University of Michigan.

* Sodium amytal was supplied by the Lilly Research Laboratories.

DOSAGE AND ADMINISTRATION

In the calculation of the dosage for this series of cases, an attempt was made to obtain the full anesthetic effect of sodium amytal consistent with safety. In view of the fact that the lethal dose for man is as yet unknown, a maximum dose of 1.6 Gm. was maintained, as suggested by the originators. A basis of 20 mg. per kilogram of body weight was set as a standard for the average person. Considering the individual variation in the effect of all hypnotics, age, general strength and debilitation were factors in determining the exact amount given some patients, the old and debilitated usually having their calculated dosage decreased from 150 to 300 mg., while young, robust persons were occasionally given from 100 to 200 mg. more. Again, if during the administration of the sodium amytal the blood pressure or the respiratory rate decreased more than usual or the patient dropped off to sleep quicker than usual, the total dosage was decreased from 100 to 300 mg.

The drug was given in our special anesthetic rooms, intravenously at the rate of 1 cc. of the 10 per cent solution per minute. A careful check on blood pressure, respiration and pulse was taken every minute during the administration and every

TABLE 1.—*Operations Performed*

Herniorrhaphy	22
Appendectomy	16
Cholecystectomy	13
Posterior gastro-enterostomy	12
Operations on the brain	11
Plastic operation on the face	8
Partial gastrectomy	7
Colostomy	6
Nephrectomy	5
Pyelolithotomy	5
Nephropexy	5
Exploratory laparotomy	5
Resection of colon for cancer	5
Subtotal thyroidectomy	4
Resection of glands of neck	4
Miscellaneous	44
Total operations	172

The youngest patient was 13 years; the oldest 79.

five minutes during the operation. The veins used frequently became thrombosed. No sloughing at the site of injection occurred.

In all cases preliminary medication consisted of morphine sulphate, 1/8 to 1/4 grain, with atropine sulphate, from 1/200 to 1/150 grain, given from one-half to one hour before the injection of the sodium amytal.

INDUCTION

As the drug was slowly injected, in from three to five minutes the patients passed gradually, quietly and surely into what appeared to be a normal deep sleep. No stage of excitement was observed. The pupils contract early and will not react to light. At first the patient can be aroused by a needle prick or shaking. As the administration is continued, these stimuli become less effective to a point simulating profound anesthesia.

PULSE, RESPIRATION AND BLOOD PRESSURE

During the administration of sodium amytal, the pulse rate increased in 124 cases an average of 15 per minute; in 25 cases there was an average decrease of 12 per minute; in 23 cases there was no change.

In 100 cases the respiratory rate increased an average of 5.7 per minute; an average decrease of 4.3 per minute occurred in 31 cases. There was no change in 41 cases. The patient's color remained good if an effort was made to keep the upper respiratory passage unobstructed by holding up the jaw and inserting a breathing tube.

A fall in blood pressure occurred in 166 cases during the administration of the drug, the average systolic reduction being 27 mm. of mercury, while the average diastolic reduction was 15 mm. of mercury. Six cases showed a slight tendency toward increase in both systolic and diastolic pressures. There was distinctly less change in the patient's blood pressure if it was normal before the administration of the anesthetic, while persons with hypertension or hypotension showed a much greater reduction. The ordinary operative trauma was a decided stimulus to the return of the blood pressure to normal. The administration of any one of the gases on hand, nitrous oxide-oxygen or carbon dioxide, was much more effective in causing the blood pressure to return to normal than was ephedrine. Sodium amytal had no tendency to keep the blood pressure of a patient with hypertension low during the operation, even though there was a decided reduction during the administration of the drug. In such cases the pressure usually rose higher during the operation. For example, in one case (no. 231429) the blood pressure varied thus: before operation, 160 systolic and 70 diastolic; during administration of anesthetic, 90 systolic and 74 diastolic, and during operation, 200 systolic and 100 diastolic.

DURING OPERATION

As a routine the operation was started within from three to five minutes from the time of completion of the administration of the drug. Into the skin and parietal peritoneum a local anesthetic was usually injected before incision. No inhalation anesthestic was given until requested by the surgeon because of (1) occasional poor relaxation, (2) a tendency for the patient to squirm under the stimulus of the incision, or (3) handling of the viscera.

Sodium amytal alone was entirely satisfactory in 42 of the cases. In 21 cases of this group major abdominal operations were performed. The intestines appeared to be collapsed and could be packed away from the operative field with more than the usual ease. Exposure was ideal. There was no increased tendency toward bleeding or oozing. Facilities for closure were perfect. The effect lasted well beyond the average time for the operation.

The remaining 130 cases required an additional anesthetic agent as shown in table 2.

In the 2 cases in which added open ether was used plastic operations were performed on the face requiring analgesia, the selection being made for convenience only. Greater relaxation was the need for adding a low grade ether vapor to the nitrous oxide and oxygen in 11 cases; in 6 of these cases the calculated dose of sodium amytal had been diminished. Accordingly, in at least 119 of 130 cases, the demand was for analgesia alone, the sodium amytal supplying the other qualifications of a good anesthetic.

The administration of nitrous oxide and oxygen was started in proportions of about 90 to 10 per cent at any time needed, and in the great majority of cases was rapidly reduced to 75:25 or lower, with satisfactory results. It could be stopped and restarted at any time during the

TABLE 2.—*Supplementary Anesthesia Used*

	Cases
Nitrogen monoxide-oxygen 90/10 per cent-75/25 per cent	112
Nitrogen monoxide-oxygen plus low grade ether vapor	11
Open ether	2
Local	4
Avertin	1
Total cases	130

operation without the patient waking up. Hyperventilation of the lungs was carried out at the end of each operation with carbon dioxide and oxygen.

Of 121 abdominal cases the relaxation was entirely satisfactory, almost to the extent of an open ether anesthesia, in 112. In 7 of the remaining 9 cases, the calculated dose of 20 mg. per kilogram was reduced from 100 to 500 mg. In this attempt to study the full value of sodium amytal as an anesthetic, we felt that the last 100 to 300 mg. of the drug added greatly to the depth of the narcosis and the degree of relaxation.

Considering the anesthesia as a whole, 160 cases were declared to be entirely satisfactory to the operating surgeon. In 6 of the remaining 12 cases, major abdominal operations were performed in which the calculated dose of sodium amytal had been decreased. During a laparotomy, in spite of the full dosage of sodium amytal supplemented by nitrous oxide and oxygen, the patient squirmed about during the whole operation. In the remaining 5 cases, in which operations on the brain were performed, there was a tendency to move the head during the operation, which was extremely disconcerting.

IMMEDIATE POSTOPERATIVE COURSE

All the patients were placed on full special or half special nursing care until they had completely reacted from the sporific effect of the drug. Special nursing was then continued or discontinued according to the general need of the patient. The blood pressure was taken every twenty minutes for the first three to four hours and every hour thereafter until the patient had reacted. Rarely did the pressure decrease enough to indicate the use of cardiovascular stimulants, and at no time was it alone a cause for alarm. Deep breathing was encouraged in all patients. In older persons this was stimulated by a few breaths of 5 per cent carbon dioxide and 95 per cent oxygen at twenty-minute intervals.

A careful check was made to determine the length of time required for these patients to react sufficiently to take fluids by mouth. This analysis is shown in table 3.

TABLE 3.—*Time of Reaction*

Hours to React	Number of Cases	Percentage		
2– 4	44	26.4		
4– 6	32	19.1	65.2%	
6– 8	33	19.7		86.2%
8–10	17	10.2		
10–12	18	10.8		
12–15	7	4.2		
15–20	11	6.6		
20–24	1	0.6		
24	4	2.4		

The longest period required to react was forty-six hours. The average age of patients reacting in twelve hours was 38 years, over twelve hours, 55 years. The great majority of patients, particularly those who had had other anesthetics previously, were enthusiastic in their praise of sodium amytal and readily agreed to have it again if necessary.

POSTOPERATIVE ANESTHETIC COMPLICATIONS

Nausea and vomiting were rarely seen; certainly, in no case in which the disease or added anesthetic would not account for it entirely.

Restlessness and disorientation were rather common findings in the first few hours; in only three cases, however, did they occur to a degree that could not be adequately handled by the special nurse and the usual postoperative narcotic treatment.

Blurring of vision was noted in two patients at intervals for the first twelve hours.

Fifty-nine of the women and 58 per cent of the men required postoperative catheterization, following the usual standing order for the surgical wards that all patients be catheterized every eight hours after

operation unless they voided voluntarily, and more frequently if more than 10 ounces (295.7 cc.) of urine was obtained. Seventy-six of the patients were catheterized only once or twice. In the whole group, 2 cases of pyelocystitis developed; in both cases herniorrhaphy had been performed, the eight hour, 10 ounce rule was not observed, and the bladder was allowed to overdistend.

The prolonged drowsiness, shallow respirations and lethary seen in these patients for a variable number of hours postoperatively would seem to add another factor in the production of postoperative infections of the respiratory tract. In 11 of our cases (6.4 per cent) definite pulmonary complications developed following abdominal operations.

TABLE 4.—*Pulmonary Complications*

Age	Operation	Sodium Amytal per Kilogram Body Weight	Supplementary Anesthesia	Complications
65	Posterior gastro-enterostomy for duodenal ulcer	17.1 mg.	N_2O-O_2	Bilateral bronchopneumonia
40	Colostomy, cancer of rectum.....	20.0 mg.	N_2O-O_2	Acute bronchitis
60	Incision and drainage of appendical abscess; bronchopneumonia	15.0 mg.	None	Terminal bilateral bronchopneumonia
39	Repair of ruptured ventral hernia; low grade bronchopneumonia	15.0 mg.	N_2O-O_2	Bronchopneumonia; no worse
48	Repair of inguinal hernia.....	20.0 mg.	N_2O-O_2	Pulmonary edema
62	Cholecystogastrostomy for cancer of head of pancreas	15.4 mg.	None	Bilateral bronchopneumonia
79	Excision; cancer of the lip.....	17.0 mg.	None	Bilateral bronchopneumonia
47	Cholecystectomy for cholelithiasis...	15.7 mg.	N_2O-O_2	Bronchopneumonia
60	Exploratory, for cancer of stomach	19.5 mg.	None	Bronchopneumonia left base
19	Repair of bilateral inguinal hernia..	20.0 mg.	N_2O-O_2	Bronchopneumonia, right base
34	Posterior gastro-enterostomy for duodenal ulcer	18.4 mg.	N_2O-O_2	Pulmonary edema

This incidence is not higher than the average in such a group and compares favorably with the incidence in this clinic with other anesthetics, as follows: series 93, ether cases, pulmonary complications, 14 (15 per cent); series 96, ethylene, pulmonary complications, 4 (4.2 per cent), and series 172, sodium amytal, pulmonary complications, 11 (6.4) per cent.

There were no deaths in this series directly attributable to the use of sodium amytal.

CONCLUSIONS

1. Sodium amytal given intravenously is a satisfactory addition to the anesthetic armamentarium.

2. It is an exceedingly agreeable form of anesthesia from the patient's point of view.

3. In consideration of the fact that 75 per cent of the patients required an additional anesthetic, we raise the question as to whether smaller doses of sodium amytal plus the additional anesthetic would not be just as satisfactory as our nearly maximal dose. This would effect a decrease in the length of time of postoperative narcosis and its consequent possible complications.

PATHOGENESIS OF HYPERNEPHROMA*

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From the numerous reports in the literature on hypernephromas, it is apparent that much confusion exists concerning both the clinical course and the pathologic variations. It is commonly believed that the hypernephroma is a highly malignant tumor and runs a rapid course. Such a concept is at variance with our findings.

We have studied a group of forty-four instances of hypernephroma observed at the Montefiore Hospital, in which autopsies were obtained in thirty-three. In the remainder, pathologic diagnoses were based on the examination of removed kidneys or on biopsies from metastases. Of this group, twenty-eight showed clinical manifestations of neoplasm. In the remaining sixteen, a hypernephroma was discovered as an accidental observation at autopsy. Such tumors were limited solely to a kidney or a suprarenal gland. The patients in this group presented no clinical evidence of a hypernephroma, and all died of other unrelated diseases in which the tumor played no apparent rôle.

The term hypernephroma is applied to neoplasms of the kidney or the suprarenal gland that are yellowish and vascular, that show a tendency toward hemorrhage, necrosis and cyst formation, and that microscopically resemble in some areas the structure of the suprarenal cortex. Histologic examination of sections from different areas of such tumors reveals marked variation in the structure and arrangement of the cellular elements. Much of the confusion in the literature has arisen from attempts to limit the criteria of hypernephromas to the tumors presenting the characteristic microscopic resemblance to the suprarenal cortical tissue. Ewing excluded from this group tumors with distinct lumina and those showing papillary structures.

Since the classic description of hypernephromas by Grawitz, a prolonged and difficult controversy as to the pathogenesis and mode of development has taken place. It is beyond the scope of this paper to discuss at any length the evidence for the origin of hypernephroma.

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* From the Surgical and Laboratory Divisions of Montefiore Hospital.
* This work was aided by a grant from the Gibson Fellowship Fund.

whether from the cortical suprarenal rest (Grawitz,[1] Chiari,[2] Beneke,[3] Pick,[4] Schmorl,[5] Askanazy,[6] Lubarsch,[7] Gatti,[8] Kelly[9] and Gerlach and Gerlach[10] or from the cells of kidney tubules (nephrogenic origin as developed by Stoerk[11]). (For a complete review of the literature see Lubarsch.[7])

Stoerk and his school based their conclusions as to the nephrogenic origin of hypernephroma on certain histologic resemblances of the individual cells and their arrangement to renal tubular epithelium. Considerable weight is added to his theory by the frequent association of papillary and adenomatous structures in true Grawitz tumors.

The adherents of the suprarenal origin of these tumors base their conclusions on the close similarity of the arrangement and appearance of the cells of the tumor to those of the fasicular layer of the cortex of the suprarenal gland and the frequency with which hypernephromas are found at the sites in the kidney where suprarenal cortical rests are common.

Pick described an instance of a ganglioma and hypernephroma in the same tumor in the kidney. The development of this unique tumor arose, in his opinion, from a suprarenal rest in the kidney containing both cortical and medullary tissue. He concluded, therefore, that this is *prima facie* evidence in support of the suprarenal origin of hypernephromas.

Gerlach and Gerlach, in a review of ten Grawitz tumors, seven suprarenal rests and three carcinomas of the kidney, concluded that the new growths arise from cortical rests. According to these observers, cortical adenomas develop from aberrant suprarenal rests. The adenoma undergoes further hyperplasia and differentiation into a hypernephroma, at first benign and then malignant. The malignant hypernephroma may assume various histologic appearances. In the same tumor may be found papillary or adenomatous structures, or the tumor may resemble a diffusely infiltrating sarcoma or carcinoma. They

1. Grawitz, Paul: Virchows Arch. f. path. Anat. **93**:39, 1883.
2. Chiari: Ztschr. f. Heilkund., 1884, vol. 88.
3. Beneke, R.: Beitr. z. path. Anat. u. z. allg. Path. **9**:440, 1891.
4. Pick, L.: Med. Klin. **23**:3 (Jan. 7) 1927.
5. Schmorl: Beitr. z. path. Anat. u. z. allg. Path., 1891, vol. 9.
6. Askanazy, M.: Beitr. z. path. Anat. u. z. allg. Path. **14**:133, 1893.
7. Lubarsch, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologische Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6.
8. Gatti, G.: Virchows Arch. f. path. Anat. **144**:467, 1895.
9. Kelly, A.: Beitr. z. path. Anat. u. z. allg. Path. **23**:280, 1898.
10. Gerlach and Gerlach: Zur Histogenese der grawitschen Tumoren der Niere, Beitr. z. path. Anat. u. z. allg. Path. **60**:383, 1915.
11. Stoerk, O.: Beitr. z. path. Anat. u. z. allg. Path. **43**:393, 1908.

expressed the belief that all these elements may arise from the same cells, and that these variations are stages in a continuous development.

Lubarsch, though favoring the suprarenal origin of hypernephromas, expressed the opinion that the papillary structures in hypernephromas are due to the growth of inclusions of kidney tubules in the anlage of the suprarenal rests which are secondarily stimulated to growth by the development of the hypernephroma. He preferred the expression hypernephroid tumor and included in this group all the hypernephromas or true Grawitz tumors. Under this term he further subdivided the Grawitz tumors into true hypernephromas, hypernephromatous adenomas, papillary adenomas and hypernephroid carcinomas.

There have been some experimental attempts to reproduce hypernephromas in animals by transplantation of cortical tissue into the kidney. For the most part, the results have been negative and inconclusive because of failure of the transplants to grow (Galleotti and Villasanta.[12]

CASES WITH CLINICAL MANIFESTATIONS

This group of cases consisted of twenty-eight instances with definite symptoms or physical signs of neoplasm. An autopsy was obtained in nineteen. In the other nine instances, a pathologic diagnosis was made by the examination of excised tissue.

The age of onset varied from 35 to 70 years, the greatest number occurring in the fifth and sixth decades. The duration of illness from the initial symptom to death ranged from six months to twenty-two years. The average duration of life after the onset of the initial symptoms was four years and four months.

The most frequent mode of onset was with urinary manifestations, such as frequency, tenesmus, nocturia, inability to void and hematuria. Abdominal pain or pain in the lumbar region was the initial complaint in a few cases. In some instances no symptoms were noted until a mass was accidentally discovered during the course of an examination, and in a few cases loss of weight and weakness were the first observations.

Very often metastatic lesions constituted the earliest evidence of disease. In some patients a pathologic fracture due to a metastatic lesion was the first indication of the presence of a malignant disease (case 10). In one instance, the first symptoms were those of a brain tumor (case 8). Especially interesting is the group of cases that masqueraded as primary tumors of the pelvic bones (cases 7, 15, 16,

12. Galleotti, Villasanta, Pandi and Imbert, quoted by Lubarsch (footnote 7).

18 and 24). One patient was treated during a period of eight years for a primary giant cell sarcoma of the ilium. This diagnosis was made on the basis of a biopsy (case 15). In one instance, the patient complained of pain in the chest and a cough for seven years prior to the onset of urinary symptoms. This was due to the presence of a pulmonary metastasis (case 20).

TABLE 1.—*Observations in Twenty-Eight Cases*

Case	Name	Sex	Age	Initial Symptoms	Operation
1	Schweig	Female	44	Metastases to spine with cord symptoms	Nephrectomy
2	Barsky	Female	53	Urinary symptoms	Nephrectomy
3	Friedland	Male	71	Painful abdominal mass and ascites	
4	Leon	Male	46	Urinary symptoms	Nephrectomy
5	Kerner	Male	57	Urinary symptoms	Nephrectomy
6	Marcus	Male	39	Metastases of pelvis and left femur	
7	Felber	Male	53	Bone metastases	
8	Markowitz	Female	53	Brain tumor	
9	Altman	Female	48	Urinary symptoms	Nephrectomy
10	Jacobs	Male	54	Bone metastases	
11	Levine	Male	50	Urinary symptoms	Nephrectomy
12	Grauer	Male	52	Urinary symptoms	Nephrectomy
13	Weichler	Male	66	Urinary symptoms	Nephrectomy
14	Bernstein	Male	70	Cord symptoms	
15	Kerling	Male	55	Tumor of right ilium	
16	Silverman	Male	51	Tumor of right ilium	
17	Leventhal	Male	53	Urinary symptoms	Nephrectomy
18	Block	Female	54	Bone metastases	
19	Epstein	Male	35	Mass in abdomen	Nephrectomy
20	Hellenthal	Male	62	Pulmonary symptoms, pain in chest and shortness of breath	
21	Heyman	Male	51	Urinary symptoms	Nephrectomy
22	Kleinerman	Female	44	Loss of weight, asthenia	
23	Leder	Male	55	Urinary symptoms	
24	Mayer	Male	44	Tumor of right hip	
25	Goldkoff	Female	46	Urinary symptoms	Nephrectomy
26	Ruff	Male	53	Urinary symptoms	Nephrectomy
27	Cruzius	Female	59	Vaginal bleeding	
28	Gross	Female	60	Urinary symptoms	

Modes of Onset

A. Urinary symptoms:
   1. Urgency
   2. Frequency
   3. Hematuria
   4. Tenesmus
   5. Inability to void
B. With pain, either abdominal or lumbar, or both
C. With the discovery of a mass in the abdomen
D. With evidence of metastatic symptoms:
   1. As a tumor of the pelvis
   2. With pathologic fracture or bone metastases
   3. Neurologic manifestations
   4. Vaginal bleeding
E. With loss of weight and cachexia

Another unusual method of onset is with vaginal bleeding (case 27). Such cases have been previously described (Gellhorn[13]). This symptom is due to invasion of the vaginal wall by retrograde extension of tumor tissue into the vaginal veins from the inferior vena cava.

RESULTS OF TREATMENT

In thirteen cases nephrectomy was performed. The duration of life following nephrectomy varied from one year and one month to

13. Gellhorn, G.: Zentralbl. f. Gynäk. **53**:527, 1929; Am. J. M. Sc. **156**:94, 1918.

seven years, with an average duration of two years. The efficacy of nephrectomy in this group of cases cannot be estimated, because all the cases had a fatal termination.

Since only about 50 per cent of cases of hypernephroma of this series began with symptoms that led to investigation of the kidneys, nephrectomy was performed only in this group. In the other group, the initial symptoms were those due to metastases and precluded the possibility of nephrectomy. A nephrectomy is rarely performed in such cases. The benefit of nephrectomy on the course of the disease is, therefore, extremely difficult to evaluate.

Roentgen therapy was of slight value, in only a few instances relieving the pain due to metastases of the bones or lungs.

TABLE 2.—*Distribution of Metastases as Determined by Autopsy and Roentgen Examinations*

	No. of Cases		No. of Cases
No metastases	15	Ribs	3
Retroperitoneal nodes	6	Heart	3
Suprarenal gland	6	Peritoneum	5
Lung	20	Thyroid	3
Left renal vein	1	Pancreas	3
Inferior vena cava	1	Diaphragm	1
Skull	5	Brain	3
Pelvis	10	Duodenum	2
Femora	7	Humerus	3
Skin	4	Spleen	1
Liver	3	Cervical nodes	1
Spine	3	Uterus	1
Spinal cord	2	Gallbladder	1
Opposite kidney	2	Small intestine	2
Sternum	2		

GROUP OF CLINICALLY UNDIAGNOSED HYPERNEPHROMAS (ACCIDENTAL FINDING)

This group is composed of sixteen cases, in fourteen of which the tumor arose in the parenchyma of the kidney, and in two, in the suprarenal gland. The ages of these patients varied from 23 to 79 (table 3). In none were there any symptoms or physical signs referable to the hypernephroma. The diameter of the tumors varied from 2 to 12 cm. These tumors resembled, both macroscopically and microscopically, the tumors found in patients with clinical manifestations of hypernephroma.

The tumors that were chance findings at autopsy illustrate all gradations and transitions from benign suprarenal cortical adenomas in the kidney or suprarenal gland to highly malignant hypernephromas. Various sections from the same tumor may show all these gradations (cases 32, 39, 42 and 44). The presence of benign cortical adenomatous tissue, malignant hypernephroma cells, alveolar structures and papillary

formations are all found in the same tumor in different areas. This point has been emphasized by Gerlach and Gerlach,[10] Bothe [14] and Ljunggren.[15]

By the ordinary criteria of a malignant condition, some of these tumors resemble the most malignant tumors. It is of significance that such highly malignant tumors may reach considerable size without presenting any clinical manifestations. Since a large portion of kidney tissue may be destroyed without impairment of function or without erosion into the pelvis, the tumor may attain considerable size before causing symptoms.

TABLE 3.—*Group of Undiagnosed Hypernephromas (Accidental Findings)*

Case	Name	Sex	Age	Primary Diagnosis*	Site and Size
29	H. H.	Female	79	C. A. C. V. D.; arteriosclerosis	Lemon-sized
30	J. M.	Male	63	Cardiac insufficiency; arteriosclerosis	Left kidney, melon-sized
31	G. R.	Male	67	Generalized arteriosclerosis; hypertrophy of prostate; bilateral hydronephrosis	Right kidney, small
32	L. F.	Female	52	Scoliosis, after laminectomy	Left kidney, 4 cm. in diameter
33	F. R.	Male	68	Carcinoma of colon	Left kidney
34	S. G.	Female	64	Hypertension; diabetes	
35	M. H.	Male	64	C. A. C. V. D.	Left kidney, 3 by 4 cm.
36	J. R.	Male	78	C. A. C. V. D.; hypertension	Left kidney, 2.5 cm.
37	M. G.	Male	23	Diabetes, cystitis	Small nodule
38	J. T.	Male	65	Fibroid phthisis	Left kidney, 2 cm.
39	I. L.	Male	62	Generalized arteriosclerosis; cardiac hypertrophy	Left suprarenal gland
40	L. F.	Male	37	Multiple sclerosis	Left kidney, 9 cm.
41	R. S.	Female	61	Endothelioma of brain	Upper two thirds of left kidney
42	L. C.	Male	68	Generalized arteriosclerosis	Left kidney, 7 by 5 by 5 cm.
43	M. L.	Male	70	Carcinoma of esophagus	Left kidney, pea-sized
44	M. F.	Male	24	Hypertension	Right suprarenal gland

* C. A. C. V. D. indicates chronic arteriosclerotic cardiovalvular disease.

Case 44 in which there was a malignant tumor of the suprarenal gland, illustrates the probable source of the malignant hypernephroma, for in both suprarenal glands in this patient, in addition to the hypernephroma, were found multiple benign cortical adenomas. It is extremely suggestive, therefore, that the hypernephroma represented a malignant transformation of a benign tumor.

COMMENT

A review of the histopathologic observations of Grawitz tumors emphasizes the marked variation in structure that may occur in the

14. Bothe, A. E.: Ann. Surg. **84**:57, 1926.

15. Ljunggren, E.: Studien über Klinik und Prognose der Grawitzschen Nierentumoren, zugleich ein Beitrag zur Frage nach der Genese der Hämaturie, Acta chir. Scandinav. **66**:1, 1930.

development and growth of a hypernephroma. In many instances all gradations from a benign cortical adenomatous structure to a highly malignant carcinomatous or sarcomatous appearance may be found in the same tumor. In addition, the almost constant occurrence of papillary structure in some areas of the hypernephroma makes any arbitrary classification on the basis of purely morphologic variations useless and unnecessary.

The examination of single sections of a hypernephroma may show a papillary adenomatous arrangement of the cells, and a diagnosis of carcinoma may be made. Further sections from other parts of the same tumor reveals its true nature. Some of the reported instances of carcinoma of the kidney may have been hypernephromas.

The histogenesis of the hypernephroma from cortical aberrant tissue is suggested from a study of the embryology of the suprarenal gland and the kidney. The cortical tissue of the suprarenal gland and the areas of the epithelial mesoderm from which the kidney develops lie closely together in embryonic life. Though the suprarenal cortex is developed from the mesothelium of the wolffian ridge in common with the ovary or the testis and though the kidney develops from the renal blastoma that lies below the suprarenal gland and is separated from it by the wolffian body, the suprarenal gland after the second month of fetal life is so closely applied to the kidney that inclusion of cortical tissue in the kidney may readily occur. In the course of development of the renal tissue, a few aberrant cells of the suprarenal tissue may become included in the kidney and remain there. It is probable that such cellular rests may later develop blastomatous characters. Gerlach and Gerlach [10] suggested that indifferent undifferentiated cells of the kidney anlage may be included in the aberrant suprarenal tissue, and that both groups of cells may develop and form the Grawitz tumor.

From our studies the hypothesis of kidney cellular inclusions in the suprarenal rest to account for the variations in structure of a hypernephroma is unnecessary. Transitions from small cells with dense cytoplasm and deeply chromatic nuclei to large foamy cortical cells may be distinguished. This is illustrated most strikingly in case 39, a hypernephroma arising in the suprarenal gland, in which the question of nephrogenic cellular inclusions is excluded. In this instance, some of the tumor cells are typical hypernephroma cells and others are cuboidal cells resembling epithelial cells. There can be no doubt that these cells are of the same origin. The dense chromatin content of the nuclei and the sparse cytoplasm of the cell with an absence of the lipoid material of cytoplasm are clearly distinguishable. The cuboidal cells have lost their characteristic arrangement and are grouped around cystlike and alveolar spaces. Similar variations occur in hypernephromas of the kidney.

The frequency of areas showing benign cortical adenomatous structures in a highly malignant hypernephroma (cases 39, 44, 2, 18 and 28) emphasizes the probable development of a malignant hypernephroma from a benign hyperplasia of a cortical rest in the kidney. In case 28, the primary tumor showed a highly malignant hypernephroma with striking pleomorphism. In the metastases in the pancreas, the tumor has a benign appearance with large blood spaces throughout the nodule. This development is analogous to the malignant transformation of adenomatous tissue in the thyroid, as emphasized by Marine.

If this concept is true, the life cycle of the hypernephroma must of necessity be extremely long. The cortical rest in the kidney, congenital in origin, may at any time in the life of the patient undergo adenomatous growth and develop into a more rapidly growing or malignant tumor. There probably are periods of arrest of such growths. This makes it almost impossible to determine the age of hypernephromas. It is partly for this reason that so large a group of accidental findings of hypernephromas may occur.

The intimate relationship between the hypernephroma and its extensive vascular supply permits an early metastatic dissemination by rupture into the thin-walled veins that are present in such numbers in the tumor. It is probable that in the cases in which metastatic lesions were present for years the metastases occurred at a stage of relatively low malignancy of the primary tumor. This is entirely analogous to certain types of thyroid carcinomas that histologically may appear adenomatous in structure with metastases of similar benign microscopic appearance. This type of tumor in the thyroid is notoriously slow in its growth and may even show histologic evidence of function.

SUMMARY

An analysis, from a clinical and pathologic point of view, of forty-four cases of hypernephroma is presented. In sixteen of these, the tumor was a chance observation at autopsy.

The neoplasm may exist for many years prior to the onset of symptoms.

There is extreme variation in the interval between the onset of symptoms and the death of the patient from the neoplasm.

In about half of the cases the primary symptoms of neoplasm were referable to metastatic lesions, such as those of the pelvis, skull, long bones, vagina and lungs.

The existence of a primary malignant neoplasm of the kidney with metastatic foci may exist for some time prior to the development of any symptoms.

All gradations from a benign structure to a malignant hypernephroma were found in the same tumor.

All types of histologic variations may occur in the same tumor, such as a cortical adenoma, a typical hypernephroma, papillary and adenomatous forms and highly malignant carcinoma and sarcoma-like infiltrations.

Comparative studies emphasize the histogenetic development of a hypernephroma from cortical aberrant tissue. Cortical suprarenal rests in the kidney may grow into benign adenomas. At any period during the life of the patient, such benign structures may become malignant. This development and subsequent metastatic dissemination proceeds at a variable rate.

APPENDIX

Histopathology.—A brief description of the histology of the tumors described is given in the following cases.

CASE 1.—S. S., a woman, aged 44, was admitted to the hospital on June 4, 1923. Her symptoms began about four years before admission with pain in the lumbar region. There were no urinary symptoms. On June 20, 1921, nephrectomy of the left kidney was performed, and also a splenectomy because of involvement of the spleen. Eighteen months after the onset, weakness of the left leg developed.

The patient died on Jan. 14, 1924.

Autopsy revealed a recurrent hypernephroma at the operative site with metastases to the peritoneum, spine and lung, compression myelitis, chronic cystitis and right pyelonephritis. The left suprarenal gland was destroyed.

Section through the primary tumor showed, in some areas, the structure of a typical hypernephroma, and in other areas, papillary formation (fig. 1).

CASE 2.—M. B., a woman, aged 53, was admitted to the hospital on June 4, 1923. Her illness began twenty-two years before admission with attacks of pain in the left loin associated with hematuria. Seven years prior to admission a mass developed in the left flank, and the patient was operated on, nephrectomy of the left kidney being performed because of a hypernephroma. Three years before admission she noticed a nodule in the left submaxillary space. Three months prior to admission lumps developed in the left side of the neck, and one month later she began to cough and had dyspnea.

Roentgen examination of the chest showed metastatic involvement.

The patient died on Jan. 14, 1924.

Autopsy revealed a recurrent tumor in the left kidney region, with metastases to the lungs, liver, spleen, right kidney, suprarenal glands, right and left, bronchi, mediastinal and retroperitoneal lymph nodes, heart, small intestine, mucous membrane of the gallbladder, the skin and the cervical and axillary nodes.

On section through a lymph node, some areas showed the structure of a typical hypernephroma. In other areas, the nuclei were much larger than usual. Other sections showed typical papillary structure.

Section through the recurrent tumor at the site of nephrectomy showed an extreme degree of malignancy with no resemblance to the typical hypernephroma, and only slight evidence of papillary structure. The tumor consisted of large numbers of irregular cells, loosely packed with very little stroma. There was

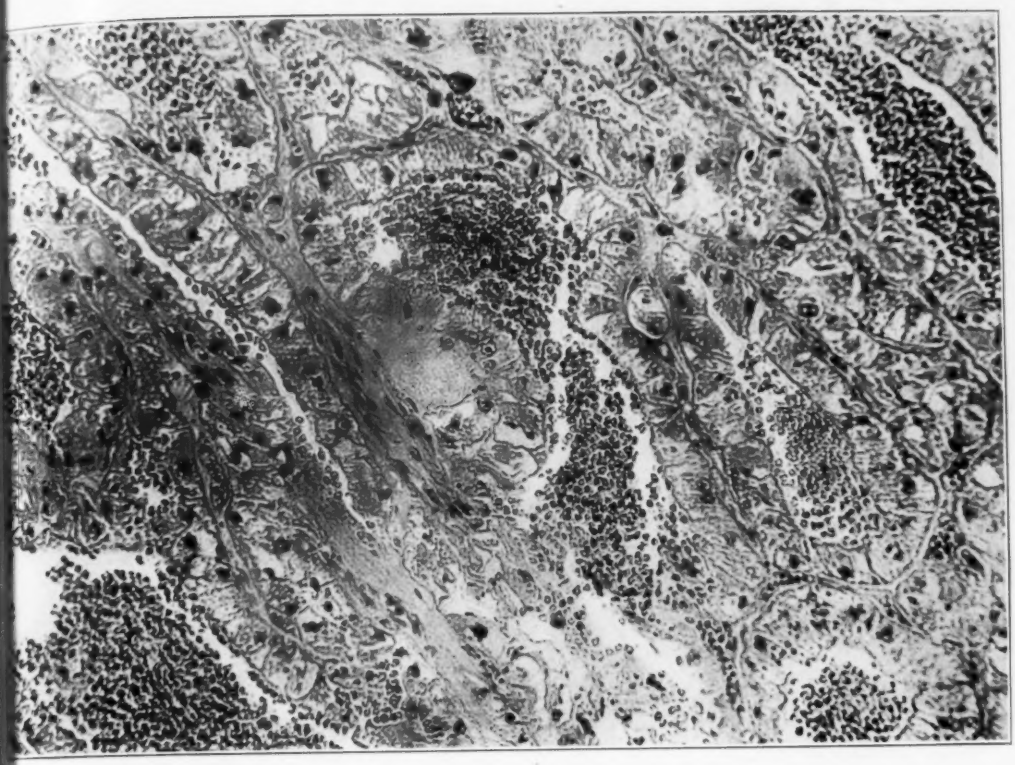

Fig. 1 (case 1).—Section through the kidney, showing glandular and papillary formation. Reduced from a magnification of × 240.

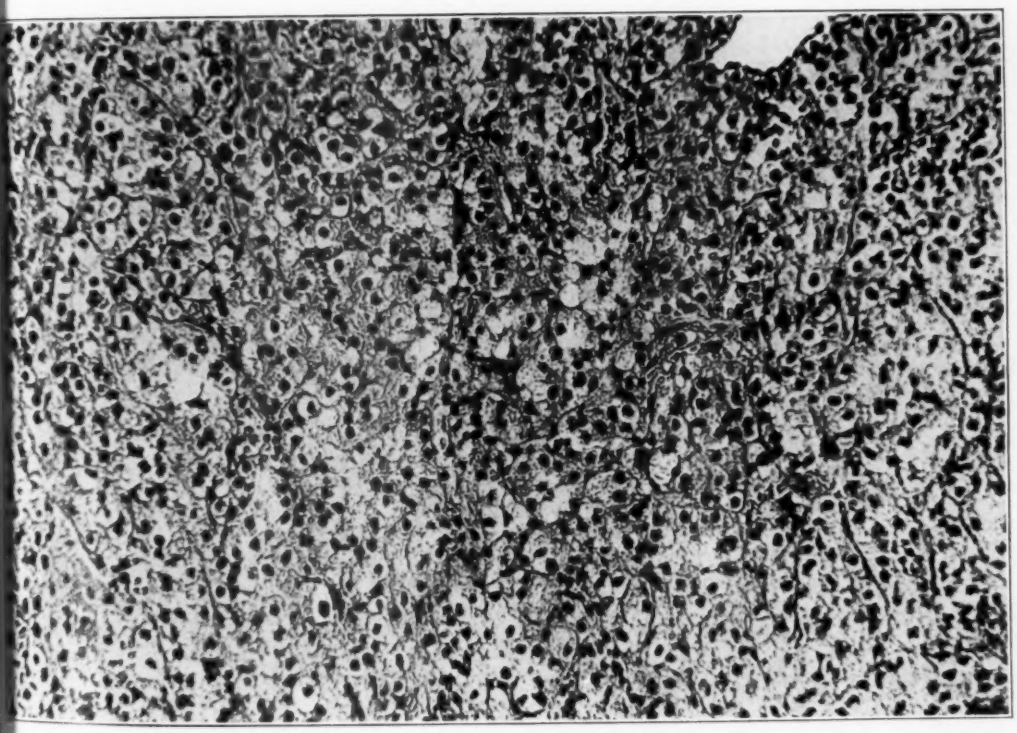

Fig. 2 (case 2).—Section through lymph node, showing a typical hypernephroma. Reduced from a magnification of × 240.

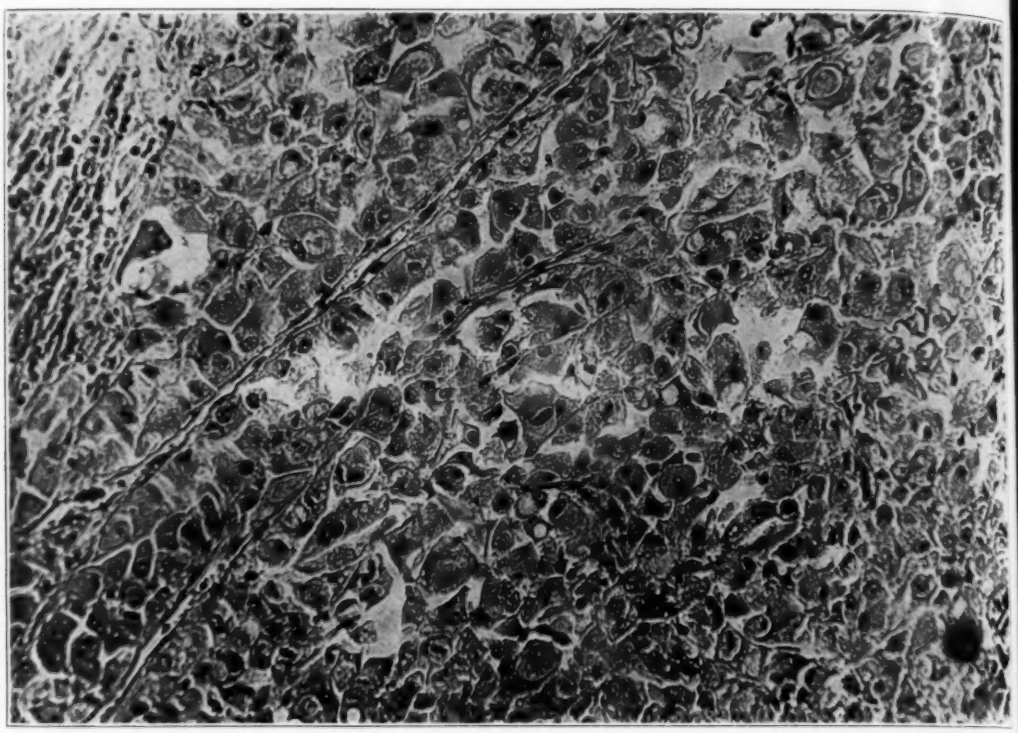

Fig. 3 (case 2).—Section through the recurrent tumor at the site of nephrectomy, showing the highly malignant structure with pleomorphism and a tendency to papillary formation. The hypernephroma character is not evident. Reduced from a magnification of × 240.

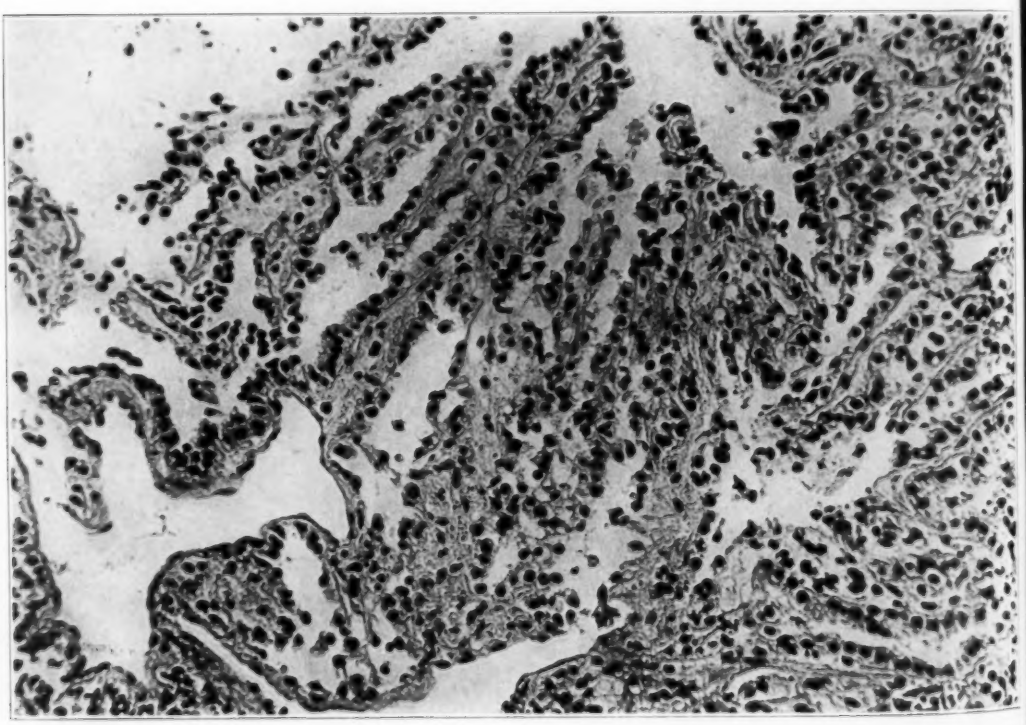

Fig. 4 (case 2).—Section through the metastatic lung, showing a predominance of papillary structure. Reduced from a magnification of × 240.

marked pleomorphism, with numerous tumor giant cells and large areas of necrosis. In the metastatic lesions, the papillary structure predominated (figs. 2, 3 and 4).

CASE 3.—P. F., aged 71, was admitted to the hospital on Feb. 2, 1916. The illness began six months previous to admission with a dull continuous pain in the iliosacral region, especially the right, with radiation down the thigh. The urine contained faint traces of albumin. Three months later the ankles became swollen, and ascites developed. At this time a mass about the size of a grape fruit was noted in the right lumbar region, with dilated veins over it. The right thigh became swollen.

The patient died on February 12.

Autopsy revealed a tumor of the right kidney, secondarily infected with metastases to the bronchial lymph nodes. The right and left renal veins and the inferior vena cava were thrombosed.

Section through the primary tumor showed a slightly atypical papillary structure with invasion of the blood vessels. The cells were much larger than those of a typical hypernephroma. The cytoplasm was pink-staining. There was a loose arrangement of the cells with marked pleomorphism and the presence of giant cells. The typical hypernephroma structure was not present.

The impression was of a highly malignant hypernephroma. The size of the cells was probably due to the imbibition of water.

CASE 4.—M. L., a man, aged 46, was admitted to the hospital on Feb. 6, 1929. His symptoms began four and one-half years prior to admission with dull pain in the left side, loss of weight and hematuria. In December, 1926, one year after the onset, the left kidney was removed for a hypernephroma. Seven months after operation, a mass recurred in the left kidney region, with hematuria.

The patient died on Sept. 6, 1929.

Autopsy showed a recurrent mass at the operative site with metastases to the lungs, liver and pleura.

Sections from recurrences at the site of nephrectomy showed nodules of cells lying in a loosely arranged connective tissue stroma with evidence of papillary structure, but no definite evidence of a typical hypernephroma.

The tumor in the kidney removed was reported as a hypernephroma.

CASE 5.—C. K., aged 57, was admitted to the hospital on March 3, 1924. The onset of the illness was five years previously with frequency of urination; one year later hematuria and pain in the hypogastrium, radiating to the lumbar regions, developed. In September, 1921, nephrectomy of the right kidney was performed because of a hypernephroma. Two years after operation, cough and dyspnea developed.

Roentgen examination showed metastases to the pelvis.

The patient died on July 25, 1925.

Autopsy revealed metastases in the lungs, suprarenal glands, left kidney, thyroid, skin, pancreas, mesentery, diaphragm, omentum and bronchial lymph nodes.

Section through the primary tumor showed it to be a typical hypernephroma with some degree of pleomorphism. The metastases showed the same structure.

CASE 6.—J. M., aged 39, was admitted to the hospital on April 22, 1928. The illness began one year before admission with progressive weakness and pain in the left thigh and buttocks and the pelvic region.

Roentgen examination of the pelvis showed a neoplasm of the right and left ilia and the upper end of the left femur.

The patient died on August 24.

Autopsy revealed a hypernephroma of the left kidney.

Sections through the primary tumor showed: In places, there were typical papillary adenomatous structures. In other areas, the cells were arranged in a mosaic, with vacuolated cytoplasm and well defined cell membranes. In some sections, the cells showed a marked absence of lipoid material with extreme pleomorphism. There were areas of hemorrhage.

CASE 7.—M. F., aged 53, was admitted to the hospital on July 22, 1926. The onset of the illness was eleven months before admission with sharp pain over the right seventh rib and pain in the right lumbar region. Examination revealed a cystic mass over the seventh rib and a mass in the left lumbar region. Three weeks before admission to the hospital, hematuria was noticed.

Roentgen examination revealed metastases to the lungs, skull and ribs.

The patient died on September 22.

Biopsy of an axillary node showed a structure typical of a hypernephroma.

CASE 8.—S. M., aged 53, was admitted to the neurologic service of the hospital on June 4, 1926, with a six months' history of headache and convulsions. A diagnosis of brain tumor was made, metastatic in character.

Roentgen examination showed involvement of the right humerus and the skull with evidence of increased intracranial pressure.

The patient died on July 7.

Autopsy revealed a hypernephroma of the left kidney, with metastases to the lungs, pancreas, duodenum and thyroid.

Section through the primary tumor showed a typical hypernephroma structure with areas of hemorrhage and necrosis and large cystlike spaces. The metastases in the pancreas showed a striking absence of lipoid material. The nuclei were much larger than in the original tumor and showed marked pleomorphism.

CASE 9.—E. A., aged 48, was admitted to the hospital on June 17, 1926, in a moribund condition, with evidence of a left hemiplegia. Three years before admission the right kidney had been removed because of hematuria, and a hypernephroma was reported to be present.

Roentgen examination showed a pathologic fracture of the right femur and metastases to the pelvis and ribs.

The patient died on June 19.

Autopsy showed a recurrent mass at the operative site with involvement of the regional lymph nodes, ribs and the right suprarenal gland.

There was a typical hypernephroma, with areas of hemorrhage. A slight degree of pleomorphism was present. In the metastases, giant cells with many nuclei were present.

CASE 10.—H. J., aged 54, was admitted to the hospital on Dec. 16, 1927. The onset of the illness was two and one-half years prior to admission with a dull ache in the left thigh followed by a pathologic fracture of the left femur.

Roentgen examination showed metastases of the left femur and the left sacrum. The left kidney was enlarged.

Biopsy of a specimen from the left femur through the neoplasm showed a hypernephroma.

The patient died on Jan. 14, 1928.

CASE 11.—F. L., aged 50, was admitted to the hospital on May 18, 1927. The onset of the illness was about two years before admission, with hematuria. Shortly after the onset, nephrectomy of the left kidney was performed because of a hypernephroma. On admission, roentgen examination showed evidence of a metastatic pulmonary and mediastinal involvement.

A typical hypernephroma was present in the kidney removed.

The patient died on Feb. 3, 1928.

CASE 12.—S. G., aged 52, was admitted to the hospital on Dec. 19, 1927, complaining of headache, weakness, loss of weight, diminished vision, dizziness, vomiting and hemoptysis. The onset of the illness was eighteen months before admission with urinary symptoms. In September, 1926, the right kidney was removed because of a hypernephroma.

Roentgenograms showed metastases to the lungs and areas of absorption in the skull.

The kidney removed was reported to contain a typical hypernephroma.

The patient was discharged from the hospital on Jan. 14, 1928.

CASE 13.—M. W., aged 66, was admitted to the hospital on May 13, 1928. The illness began three years previously with retention and bloody urine. In December, 1927, the left kidney was removed for a hypernephroma. The patient entered the hospital because of paralysis of both legs, evidence of a compression myelitis and a nodule in the thyroid.

Roentgenograms showed metastatic involvement of the fourth dorsal vertebra.

The kidney removed was reported to contain a typical hypernephroma.

The patient was discharged from the hospital on June 2, 1928.

CASE 14.—B. B., a man, aged 70, was admitted to the hospital on July 5, 1928. The onset of the illness was four months before admission with evidence of compression myelitis. He complained of inability to use his legs and of incontinence of urine and feces. Examination revealed a mass over the thoracic spine and the lower ribs.

The patient died on September 9.

Autopsy showed a hypernephroma of the right kidney with local extension and invasion and metastases to the spinal cord.

The hypernephroma was typical with areas of hemorrhage and necrosis. In some areas there was papillary formation with some degree of pleomorphism of the nuclear elements. There was capsule formation around the tumor.

CASE 15.—A. K., a man, aged 55, was admitted to the hospital on Feb. 1, 1929. The illness began eight years previously with pain in the right buttock radiating down the right thigh and swelling of the right hip. He received roentgen therapy to the right hip, a diagnosis of endothelioma having been made. Six months before admission, masses had developed on the sternum, the right axilla and in the skull, the latter pulsating.

The patient died on April 3.

Autopsy revealed a hypernephroma of the right kidney with metastases to the left kidney, sternum, ribs, cranium, right ilium and ischium, pubis, lungs and right suprarenal gland.

Section throughout the tumor of the kidney showed a typical hypernephroma. There were several adenomas in the right suprarenal gland.

CASE 16.—B. S., aged 51, was admitted to the hospital on Aug. 6, 1929. The onset of the illness was fifteen months before admission with pain in the right hip, right leg and foot. About five months prior to admission a swelling of the right hip developed.

The patient died on Feb. 8, 1930.

Autopsy showed a hypernephroma of the right kidney with metastases to the lungs, right ilium and sacrum.

Section through the kidney showed a typical benign suprarenal adenomatous structure with a slight degree of pleomorphism of the nuclear elements. In places there were large irregular spaces with areas of hemorrhage. In another section, the cells were less polyhedral and more cuboidal. They formed irregular cystlike

spaces into which the tumor extended as irregular papillary projections. The metastatic lesions had a typical hypernephroma structure.

The hypernephroma showed transitions from a benign to a malignant neoplasm, with variations in the structural arrangement of the cells.

CASE 17.—H. L., aged 53, was admitted to the hospital on Dec. 2, 1928. The onset of the illness was twenty-three months before admission with pain in the left lumbar region, loss of weight and hematuria. Six months later, nephrectomy of the left kidney was performed because of a hypernephroma. Following operation abdominal pain, dyspnea, cough and hemoptysis developed.

Roentgenograms showed metastatic involvement of the lungs and mediastinum and a pathologic fracture of the left seventh rib.

The report of examination of the kidney removed was that of a hypernephroma

The patient died on March 4, 1929.

CASE 18.—S. B., aged 54, was admitted to the hospital on Sept. 12, 1925. The onset of the illness was seven months previously with pain in the right lower extremity and back and loss of weight.

Roentgen examination showed metastatic involvement of the skull, right os pubis and right and left femora.

The patient died on November 22.

Autopsy revealed a hypernephroma of the right kidney with metastases to the lungs.

Sections from the primary tumor in the kidney showed areas of a typical hypernephroma with pleomorphism and hemorrhage. In other sections, the tumor had an adenomatous and papillary structure. In still other sections, the cells of the tumor lay free in a very loose connective tissue stroma. Here the cells showed marked pleomorphism. These areas were definitely demarcated from the more typical hypernephroma tissue by a distinct capsule. In still other areas, the hypernephroma had a definitely benign appearance, the structure closely resembling cortical adenoma. This case, like case 31, showed all gradations from benign to malignant hypernephroma, papillary adenomatous structure and highly malignant invasive carcinoma-like tissue (figs. 5 and 6).

CASE 19.—M. E., a man, aged 35, was admitted to the hospital on Feb. 19, 1918. The onset of the illness was two years before admission with pain in the right hip and a mass in the left side of the abdomen. Nine months before admission, the left kidney was removed because of a hypernephroma. Five weeks after nephrectomy the patient began to limp, and he complained of pain radiating down the left leg. A swelling developed over the right hip.

The patient died on June 20.

Autopsy revealed a recurrent tumor at the site of the left kidney with metastases to the retroperitoneal, iliac and inguinal lymph nodes, skull, lungs, liver, right ilium and femur and the skin.

The diagnosis was a hypernephroma with papillary structure and extensive necrosis, hemorrhage and formation of cystlike spaces. The recurrent tumor at the site of nephrectomy showed a diffuse, loosely arranged, cellular mass with very little stroma. The cells were large and irregularly round and showed marked pleomorphism.

There was a highly malignant structure in the recurrent tumor.

CASE 20.—B. H., aged 62, was admitted to the hospital on July 4, 1918. The illness began seven years before admission with pain in the right side of the chest

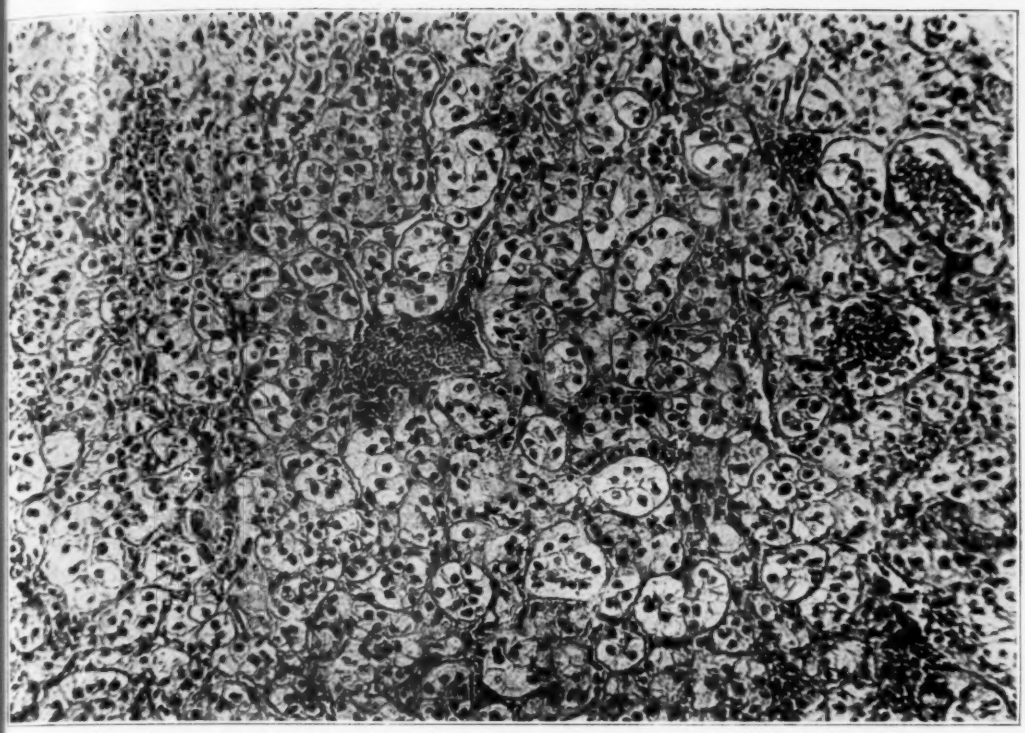

Fig. 5 (case 18).—Section through the primary tumor, showing a benign hypernephroma. Reduced from a magnification of × 240.

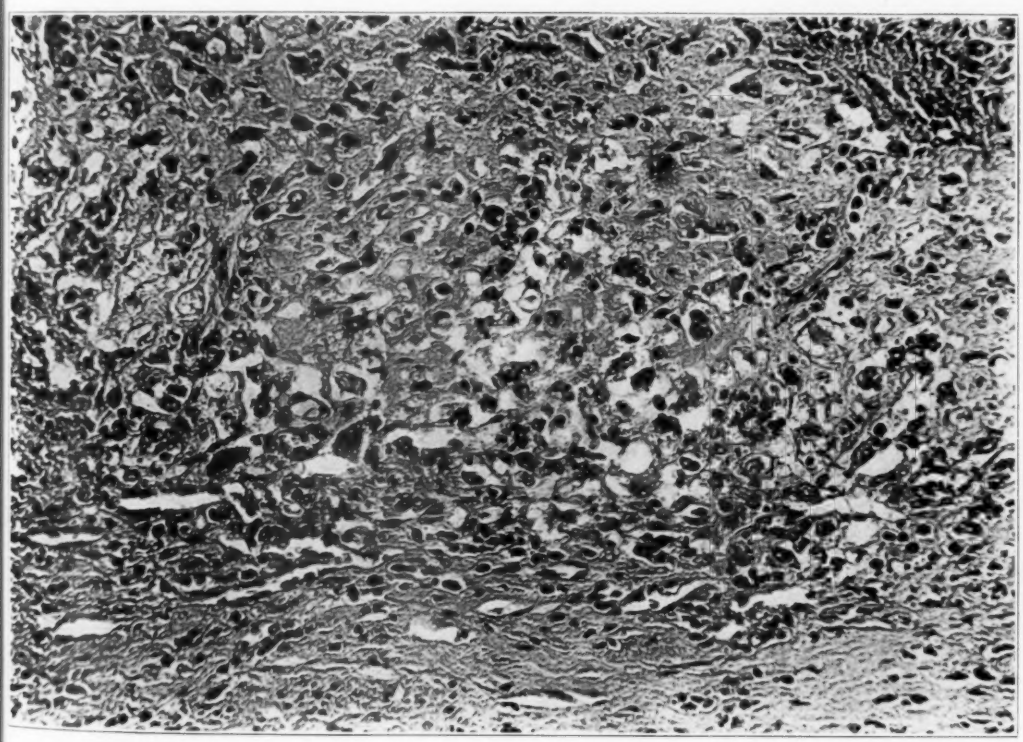

Fig. 6 (case 18).—Another section through the same tumor, as in figure 5, showing a highly malignant structure, resembling a carcinoma. Reduced from a magnification of × 240.

and shortness of breath. Three years prior to admission weakness, loss of weight and appetite, constipation and abdominal pain developed. One year later the patient noticed dysuria and hematuria.

Roentgen examination showed a dense shadow in the lower lobe of the right lung and apical infiltrations.

The patient died on November 13.

Autopsy revealed a hypernephroma of the right kidney with pulmonary metastases.

Section of the tumor showed a typical hypernephroma.

CASE 21.—L. H., aged 51, was admitted to the hospital on Nov. 30, 1922. The onset of the illness was two years before admission with hematuria. One year after the onset, the left kidney was removed because of a hypernephroma. On admission, the patient complained of pains in both lower extremities, difficulty in walking, weakness and loss of weight.

Roentgenograms showed metastatic involvement of the lungs, left ilium and ischium, the neck of the right femur and the ninth dorsal vertebra.

The kidney removed was reported to contain a hypernephroma.

The patient died on December 30.

CASE 22.—M. K., aged 44, was admitted to the hospital on Oct. 29, 1922, with a three months' history of loss of weight, asthenia, cough and expectoration. On examination, a mass was found in the left side of the abdomen.

Roentgen examination of the chest showed a mass in the mediastinum and invasion of the lung. An exploratory operation revealed an inoperable tumor of the left kidney from which a specimen of tissue was removed.

Biopsy of a specimen of the tumor of the kidney removed at operation showed a typical hypernephroma.

The patient died on Jan. 23, 1930.

CASE 23.—Z. L., aged 55, was admitted to the hospital on Aug. 8, 1922. The onset of the illness was eleven months prior to admission with attacks of hematuria. Eight months before admission the patient began to cough; he was admitted to the tuberculosis division with a diagnosis of pulmonary tuberculosis.

The patient died on April 17, 1923.

Autopsy revealed chronic pulmonary tuberculosis, tubercles in the kidney and meninges, tuberculosis of the ilium and colon and a hypernephroma of the right kidney. The bleeding was apparently due to the hypernephroma.

There was an atypical hypernephroma structure with marked pleomorphism of the nuclear elements and some degree of papillary formation. Though the cells were larger than those generally found in the more typical hypernephroma, the general arrangement of these cells in a mosaic with a network of fine connective tissue containing many capillaries definitely established the diagnosis of a hypernephroma.

CASE 24.—A. M., aged 44, was admitted to the hospital on March 6, 1924. The onset of the illness was one month prior to admission with inability to walk, pain in the legs and pain and swelling of the right hip.

The patient died on March 21.

Autopsy revealed a hypernephroma of the right kidney, with metastases to the heart, regional and distal lymph nodes, lungs, left suprarenal gland, right hip and sternum.

Section from the tumor of the kidney showed a typical hypernephroma. There were cystlike spaces and areas of necrosis. In other areas, the hypernephromatous structure was completely replaced by irregular papillary formation, showing

marked pleomorphism of the columnar cells lining the papillae. In still other areas, the tumor had the appearance of a highly malignant invasive sarcomatous structure with areas of necrosis and marked pleomorphism of the cells. In the metastases, the hypernephromatous structure was not present, but the cells were arranged in irregular, solid alveoli, separated by thin septums of connective tissue. Many giant cell forms were present.

The diagnosis was: hypernephroma with extreme variation in structure and arrangement of the cellular elements (figs. 7, 8, 9 and 10).

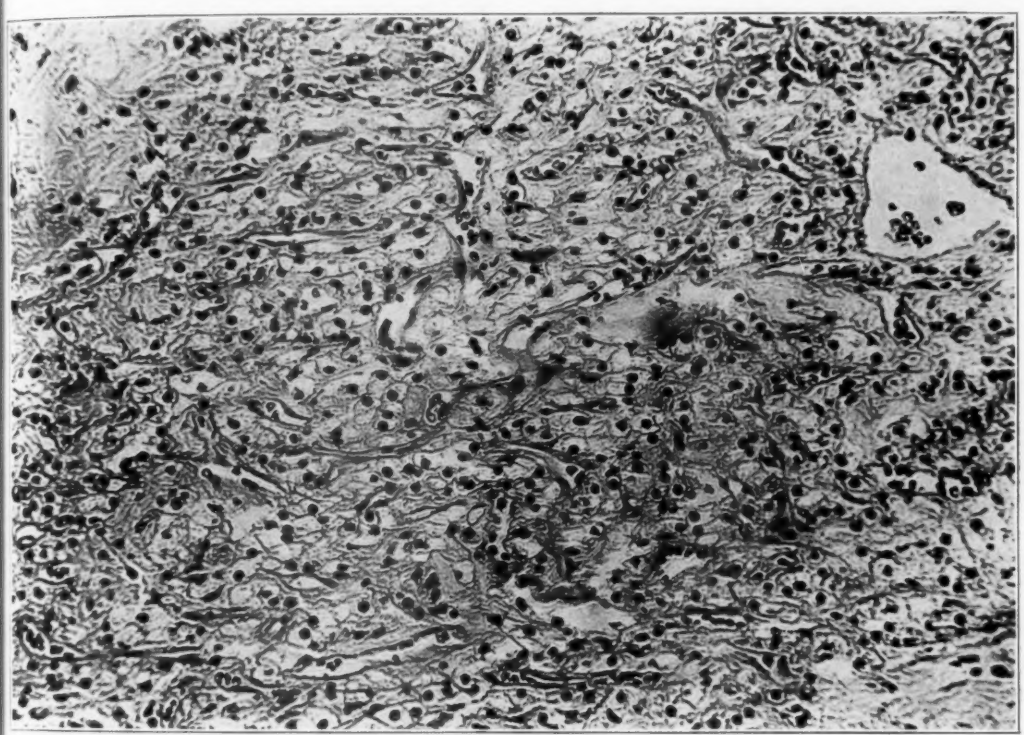

Fig. 7 (case 24).—Section through the tumor of the kidney, showing a typical hypernephroma with small cystlike spaces. Reduced from a magnification of × 240.

CASE 25.—E. G., aged 46, was admitted to the hospital on March 15, 1924. The illness began four years before admission with pain in the left side of the abdomen and urinary frequency. In November, 1922, nephrectomy of the left kidney was performed because of a hypernephroma. On admission to the hospital, there were evidences of local and peritoneal recurrences.

The kidney removed showed a hypernephroma.

The patient died on April 16, 1924.

CASE 26.—D. R., aged 53, was admitted to the hospital on July 1, 1924. The onset of the illness was eighteen months before admission with lumbar pain and hematuria. In June, 1923, the left kidney was removed because of a hypernephroma.

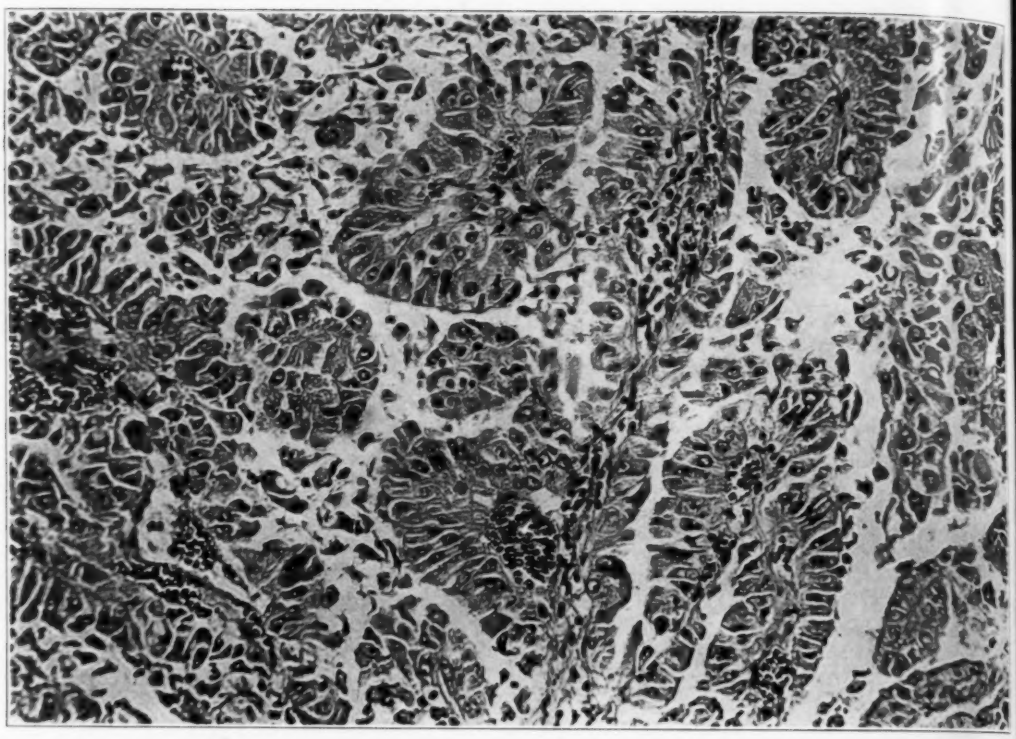

Fig. 8 (case 24).—Section through the same tumor as in figure 7, showing papillary formation with pleomorphism of the cells. Reduced from a magnification of × 240.

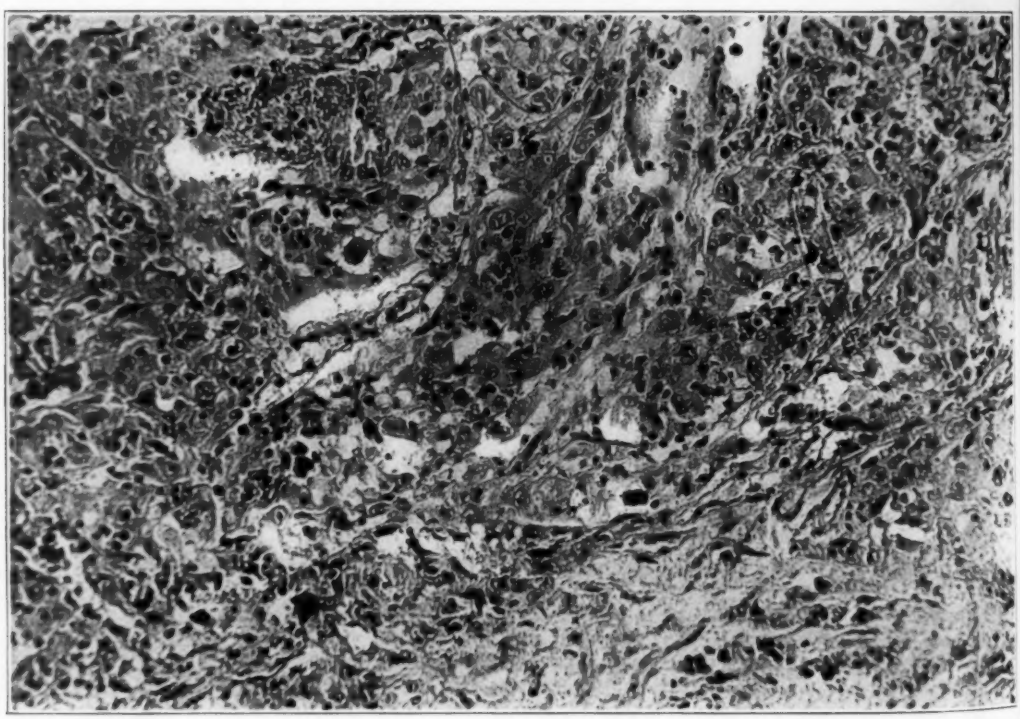

Fig. 9 (case 24).—Section through the same tumor as in figure 7, showing the highly malignant character of hypernephroma cells. Reduced from a magnification of × 240.

The kidney removed showed a hypernephroma.

The patient died on Dec. 6, 1924.

CASE 27.—C. C., aged 59, complained of vaginal bleeding. On examination, a small friable mass extending from the posterior vaginal wall was found.

Tissue taken for a biopsy from the posterior vaginal walls showed the structure of a hypernephroma.

CASE 28.—R. G., aged 60, was admitted to the hospital on Nov. 14, 1929. The illness began five years prior to admission with hematuria. One month before admission the patient sustained a pathologic fracture of the right femur.

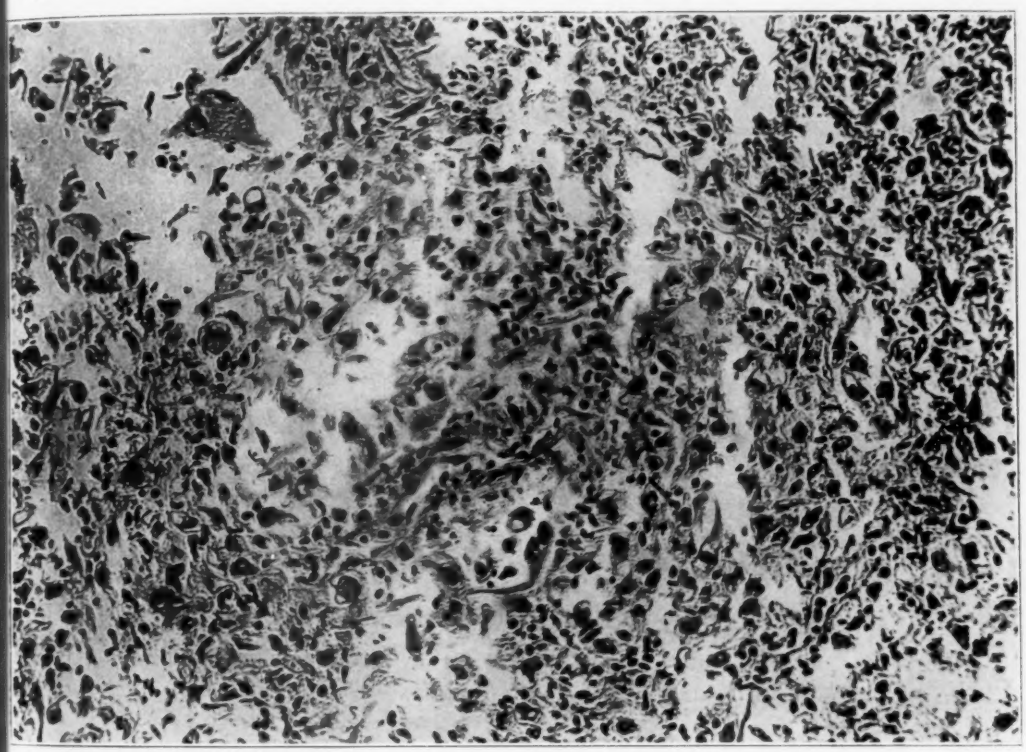

Fig. 10 (case 24).—Loose arrangement of the cells, showing marked pleomorphism and sarcoma-like structure. Reduced from a magnification of × 240.

Roentgen examination showed metastases of the right humerus, the soft parts of the chest and the right femur, with a pathologic fracture.

The patient died on Sept. 15, 1930.

Autopsy revealed metastases of the skin, peritoneum, myocardium, lungs, duodenum, pancreas, ilium, mesentery and thyroid. The right kidney was the seat of a hypernephroma.

In some areas a structure of typical hypernephroma was seen, with marked pleomorphism in other sections. The hypernephroma structure was lost near the edge of the tumor, where the cells grew individually, presenting the picture of a sarcoma with marked pleomorphism. Transitions from the more benign to the

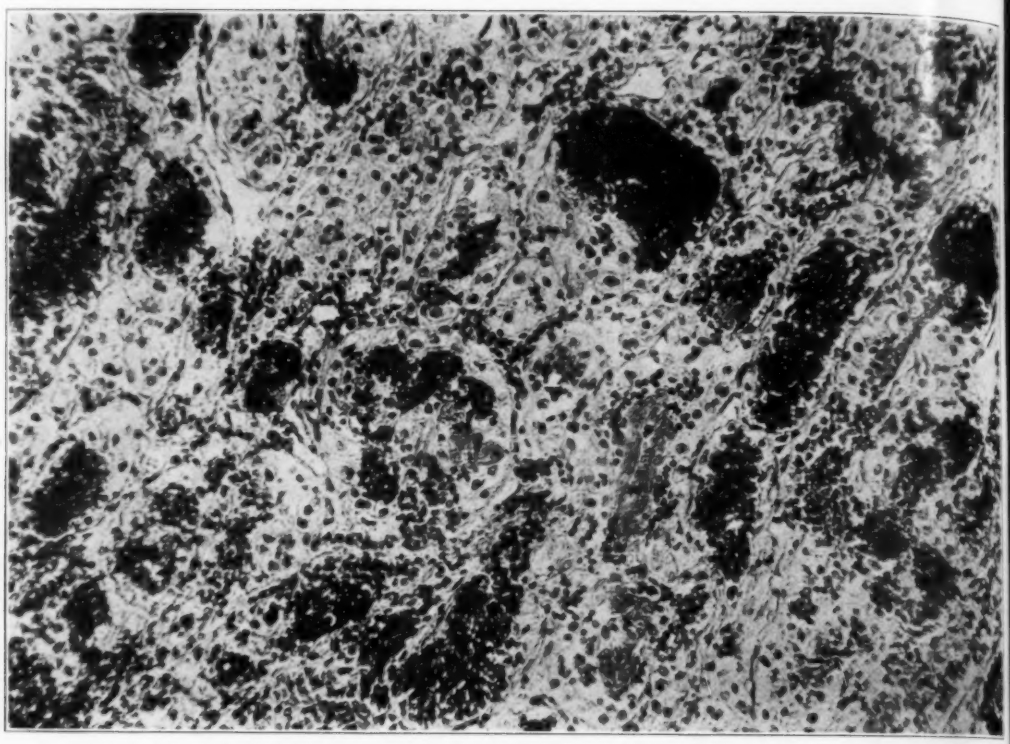

Fig. 11 (case 28).—Section through the metastasis in the pancreas, showing the benign appearance with large blood spaces throughout. Reduced from a magnification of × 220.

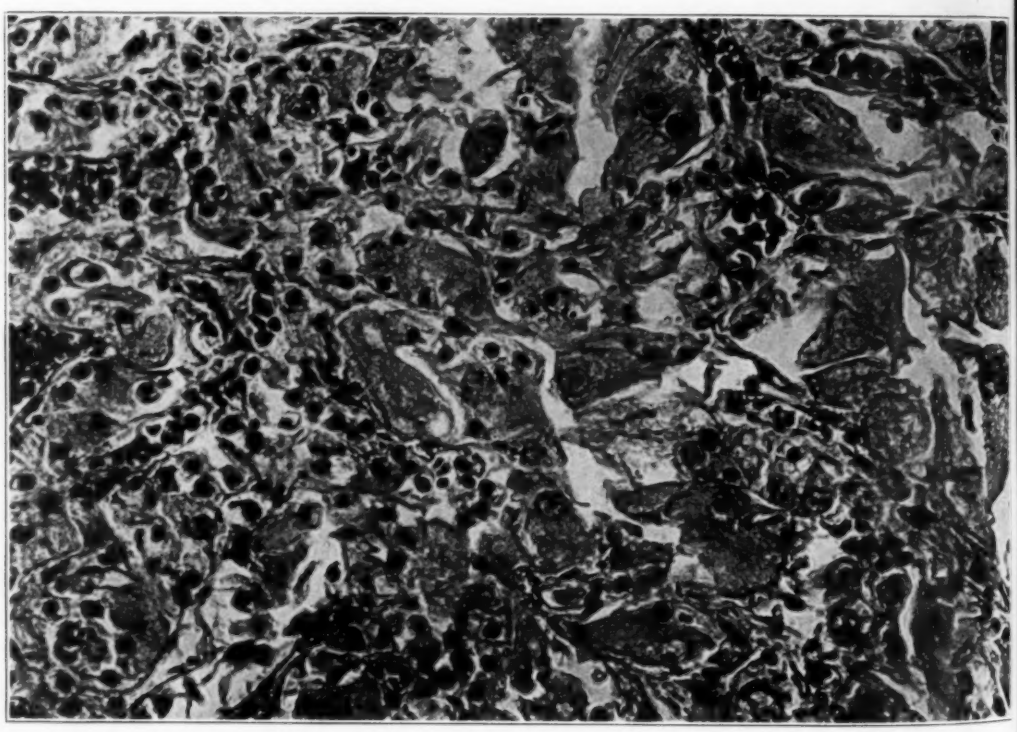

Fig. 12 (case 28).—Section through the edge of the tumor, showing marked pleomorphism of the cells with ganglion-like structure. Reduced from a magnification of × 440.

highly malignant invading cells were seen. Papillary structures were present in other sections. In the metastases all gradations were present. In the pancreas, the metastases had a benign appearance with large blood spaces throughout the nodule (figs. 11, 12 and 13).

CASE 29.—H. H., a woman, aged 79, who died of arteriosclerotic heart disease, presented a lemon-sized tumor in the left kidney. On section, there were groups of closely packed polygonal cells arranged in strands and sheets with a fine network of capillaries and connective tissue. The nuclei were small, round and eccentric. The cytoplasm was extremely foamy. In other areas, there was a typical papillary structure. The papillae were composed of two or three layers

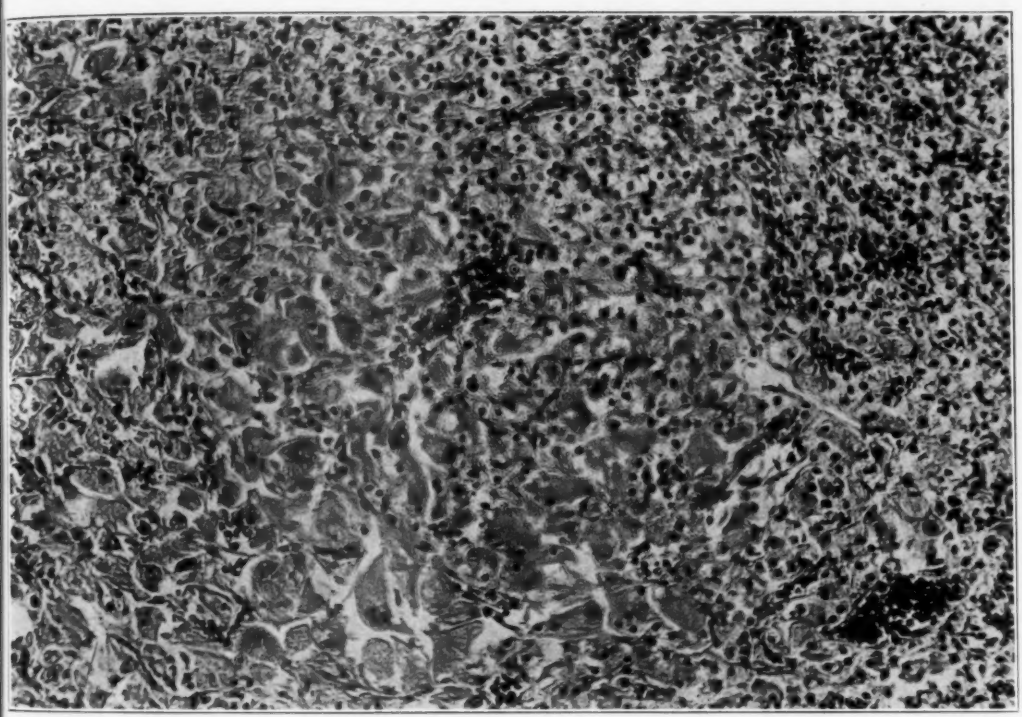

Fig. 13 (case 28).—Section showing the transition from hypernephroma to highly malignant carcinomatous appearance. Reduced from a magnification of × 220.

of cuboidal and polygonal cells lining a fine connective tissue stalk. The nuclei were large and rich in chromatin. There were many cystlike spaces. Some of these contained blood.

Sections from some areas showed the structure of a typical hypernephroma. In other areas the structure resembled that of a papillary carcinoma (figs. 14 and 15).

CASE 30.—J. M., a man, aged 63, who died of cardiac insufficiency and arteriolosclerosis, presented a tumor, the size of a lemon, in the left kidney, a typical hypernephroma. The cells were fairly uniform in size, and were arranged in columns and sheets with a fine network of connective tissue containing capillaries.

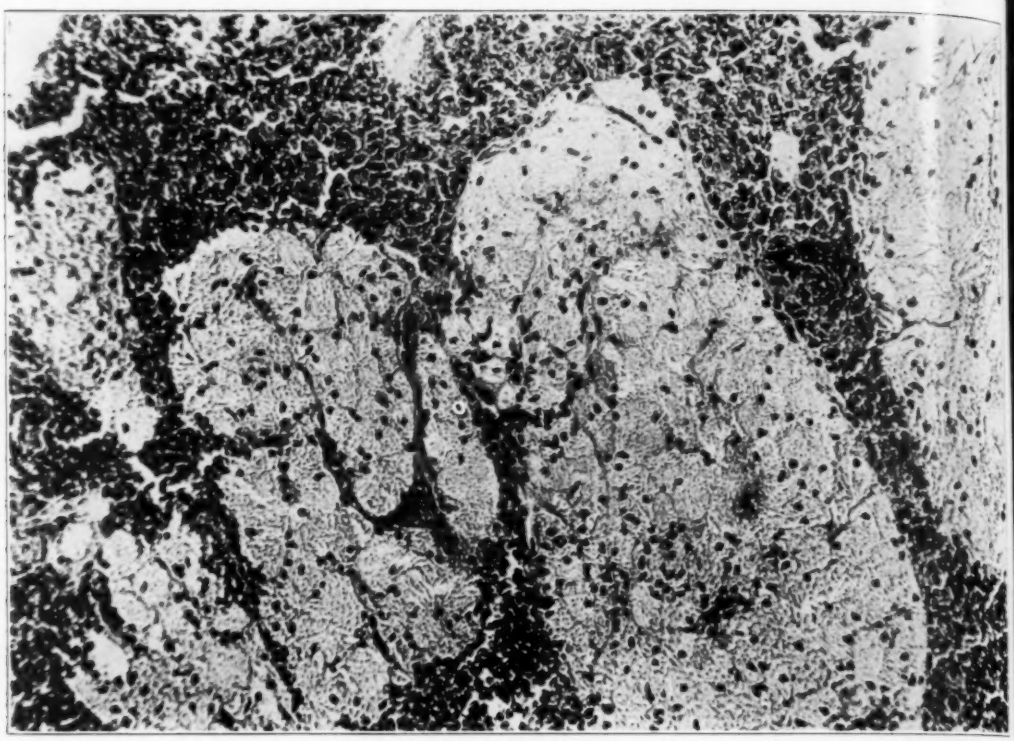

Fig. 14 (case 29).—Cells arranged as in a typical hypernephroma. The darker staining cells are masses of tumor cells arranged in solid sheets and containing little lipoid material. Reduced from a magnification of × 240.

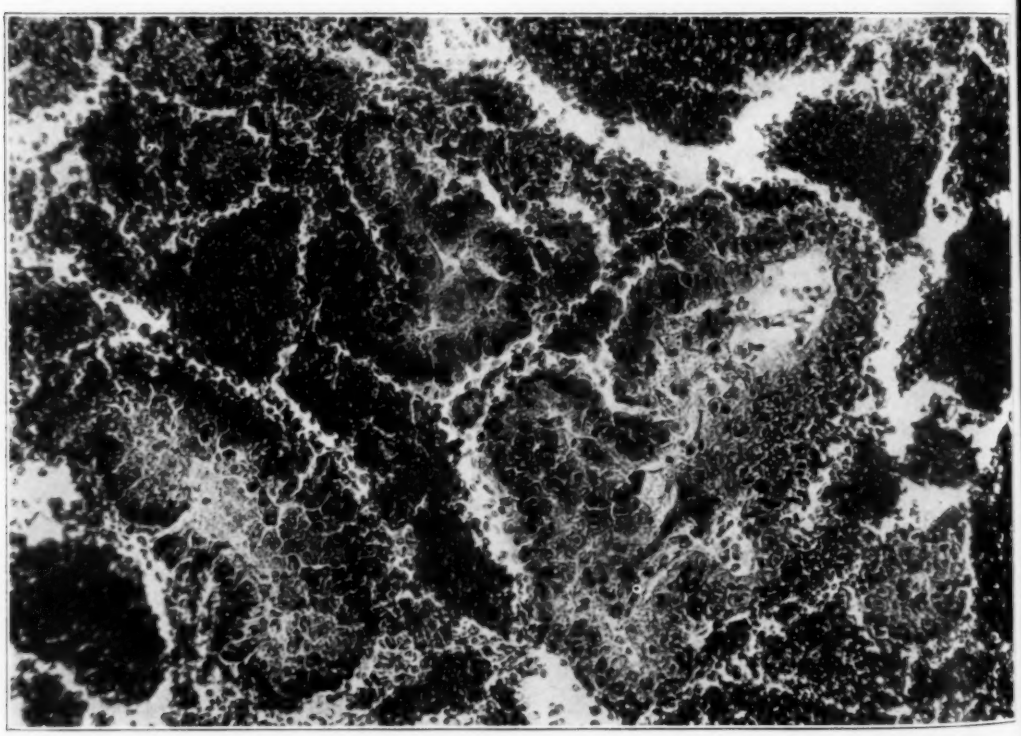

Fig. 15 (case 29).—Section through another portion of the same tumor as in figure 14, showing the papillary carcinomatous appearance. Reduced from a magnification of × 240.

In some areas the cells formed pseudo-alveoli. There was a thin capsule surrounding the tumor. The adjacent kidney tissue was compressed. This tumor gave the impression of a relatively benign growth.

CASE 31.—G. R., a man, aged 67, died of generalized arteriosclerosis, hypertrophy of the prostate and bilateral hydronephrosis. A small tumor was found in the right kidney. On section, there were several irregular masses of cells surrounded in part by a connective tissue capsule and compressing the surrounding kidney tissue. The cells were arranged in solid plates and cords, forming in places pseudo-alveolar structures. There were large cystlike spaces, areas of hemorrhage and cavernous spaces filled with blood. The cells were polyhedral and round, and the cytoplasm was pale-staining. The nuclei were small, deeply chromatic and eccentric. In places the cells were arranged in columns, separated by finely dilated capillaries. In other areas, the cells showed a loss of definite arrangement, growing widely in a loose stroma. They showed a moderate degree of pleomorphism. This was a malignant hypernephroma.

CASE 32.—L. F., a woman, aged 52, died following a laminectomy for a suspected cord tumor. In the left kidney, there was a small tumor, 4 cm. in diameter; it was sharply defined, with a fine capsule. The tumor consisted of polyhedral cells arranged in columns separated by fine connective tissue septums containing capillaries. In some places, the appearance was that of typical suprarenal cortical tissue. In other areas, the cells were more irregular and closely packed and contained less lipoid material. In these areas there were hemorrhage, necrosis and degeneration. This was a typical hypernephroma.

CASE 33.—F. R., a man, aged 67, died of carcinoma of the colon. A small tumor of the left kindey was found at autopsy.

On section, in many areas the appearance was that of a typical hypernephroma. There were other areas, however, where the cells were irregular with closely packed nuclei, showing marked pleomorphism. Hemorrhages were present. This was a malignant hypernephroma.

CASE 34.—S. G., a woman, aged 64, died of hypertension and diabetes. A small tumor was found in the right kidney.

The nodule consisted of pyramidal cells arranged in large sheets with a fine connective tissue stroma containing capillaries. The cells were foamy and contained small eccentric nuclei. In the central portion of the nodule there were numerous cystlike spaces. There was no sharply defined capsule. The cells invaded the medulla of the kidney. The walls of the several veins were invaded by hypernephroma cells.

This was a typical hypernephroma. Though invasion of the walls of the veins is found occasionally in benign adenomas of the suprarenal cortex, this may be an indication of a malignant condition (fig. 16).

CASE 35.—M. H., a man, aged 64, died of arteriosclerotic heart disease. There was a tumor in the left kidney, 3 by 4 cm. It was composed of a highly cellular tissue, in places forming pseudo-alveoli. Very little connective tissue stroma was present. The tumor cells were irregular, round and polyhedral. They did not contain a large amount of lipoid material. Many of the nuclei showed a moderate degree of variation. There were areas of hemorrhage.

Grossly, the tumor was yellowish and resembled suprarenal cortical tissue. Although it was not a typical hypernephroma, the gross appearance and some of its histologic characters warrant its inclusion in this group. The tumor may be an adenoma with fatty cells.

Case 36.—J. R., a man, aged 78, died of hypertension and arteriosclerotic heart disease. There was a tumor 2.5 cm. in diameter in the left kidney.

On section in some areas, the structure was of a typical hypernephroma with the regular arrangement of polyhedral cells and fine capillaries. In other places, there were definite papillary structures and pseudo-alveolar formation.

Case 37.—M. G., a man, aged 23, died of diabetes, cystitis and pyelonephritis. There was a small tumor in the right kidney.

In the wall of a large abscess of the kidney there was found a group of cells having the typical appearance and arrangement of hypernephromatous cells. The

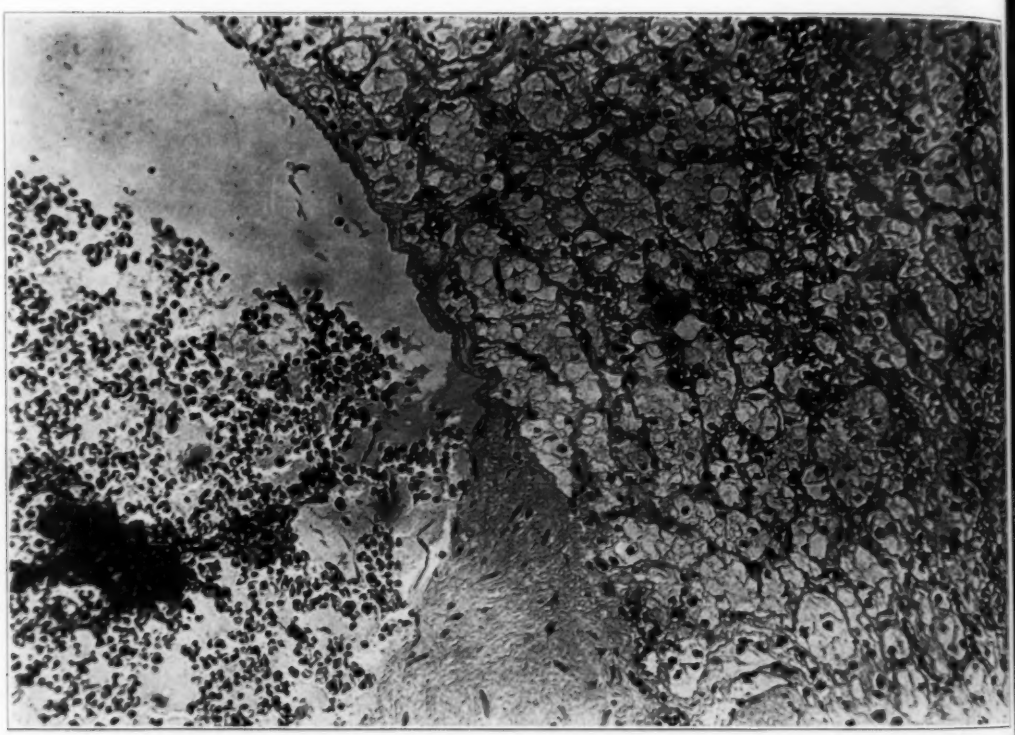

Fig. 16 (case 34).—Section through the wall of a venous space, showing invasion of the wall with hypernephroma cells. Reduced from a magnification of × 240.

extensive amount of necrosis and destruction due to secondary infection prevented more detailed study of the tumor. This was a typical hypernephroma with secondary infection.

Case 38.—J. T., a man, aged 65, died of fibroid phthisis. A tumor 2 cm. in diameter was found in the left kidney.

Section consisted of a nodule of cells surrounded by a thin capsule of connective tissue. The surrounding kidney tissue was compressed. The nodule was composed of large numbers of polyhedral cells arranged in a mosaic and in columns separated by fine capillary connective tissue. The cytoplasm in the cells was vacuolated and foamy. The nuclei were eccentric and small, but showed some

degree of variation in size. In places a definite formation of lumina was seen, and the cells had an alveolar arrangement. In other places, cystic areas with hemorrhage were present. Hemosiderin pigment in large amounts lay in and between the cells. This was a typical malignant hypernephroma.

CASE 39.—I. L., a man, aged 62, died of arteriosclerotic heart disease and hypertension. At autopsy, a small Grawitz tumor was found in the left suprarenal gland.

A typical hypernephroma with large sheets of foamy pyramidal cells possessing eccentrically placed nuclei and a fine supporting connective tissue stroma were seen. In the central portion of the tumor, there were several large cystlike spaces filled

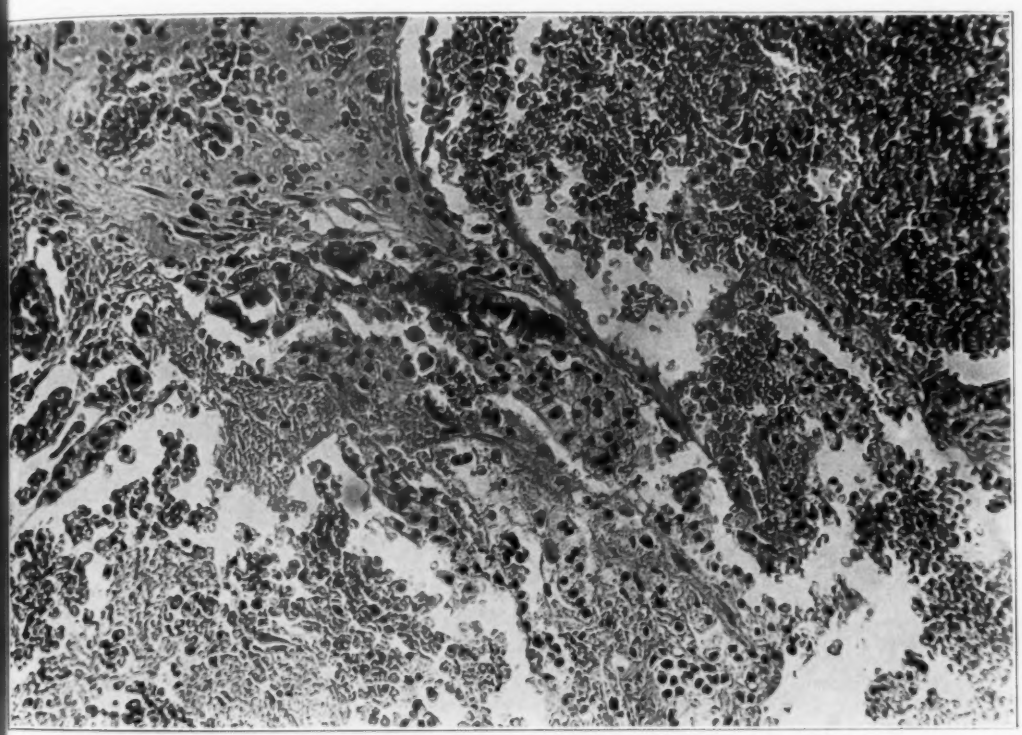

Fig. 17 (case 39).—Section showing the transition of the character of the tumor cells from typical foamy hypernephroma cells to the cuboidal "epithelial" cells lining cystlike spaces. The increase in chromatin content of the nuclei is clearly seen. Reduced from a magnification of × 240.

with blood and serum. There were gradations from islands of hypernephroma cells in clumps to isolated small islands lying in a homogeneously staining stroma. Here the honeycombed character of the cells was lost, the cytoplasm became pink-staining, and the cells became cuboidal and cylindric, losing their polyhedral character. The tumor that was definitely of suprarenal origin showed some of the glandlike appearance commonly observed in hypernephroma of the kidney.

This was an adenoma of the suprarenal gland, showing early changes of malignancy with the development of papillary structure (figs. 17 and 18).

Case 40.—L. F., a man, aged 37, died of multiple sclerosis. A tumor, 9 cm. in diameter, was found in the left kidney.

Section consisted of large numbers of polyhedral cells arranged in a mosaic, and in places in irregular alveolar formation. The stroma was extremely scant and formed a fine network containing numerous distended capillaries. In some areas the cells appeared in small clumps, particularly, and at the periphery of the nodule they lay free in a loose stroma. The cells were large and vesiculated; the nuclei were eccentric and varied in size and chromatin content. In some areas they were larger and contained two nuclei. The cells in general were somewhat larger than those in the typical hypernephroma. This was a malignant hypernephroma.

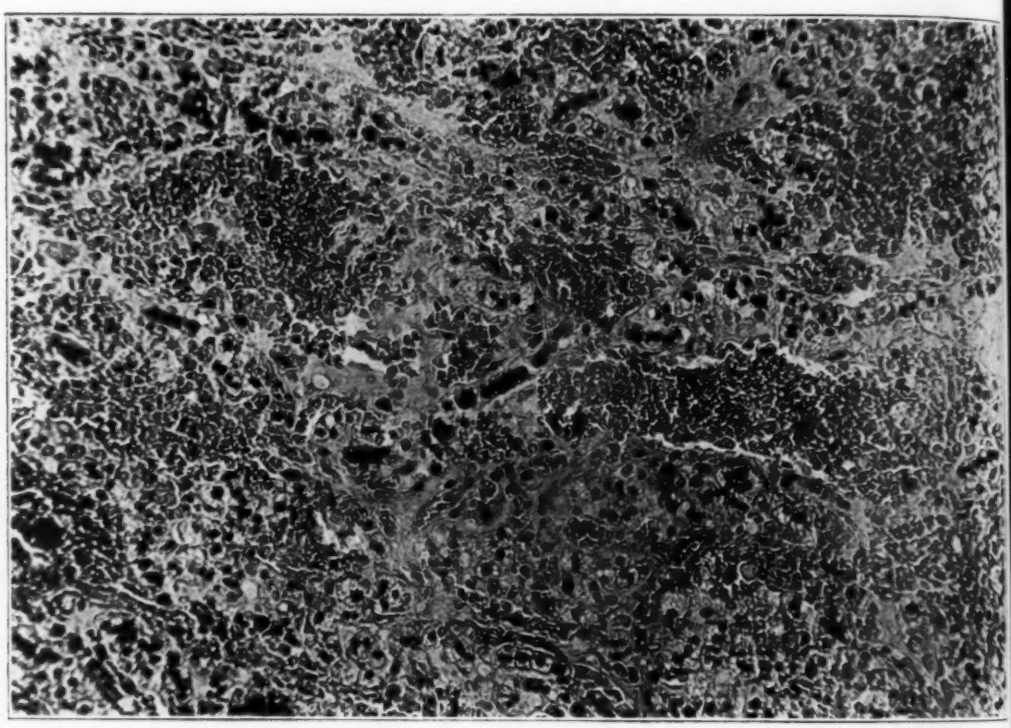

Fig. 18 (case 39).—Section showing large cystlike spaces filled with blood with strips of cuboidal cells such as are seen in figure 4. Reduced from a magnification of × 240.

Case 41.—R. S., a woman, aged 61, died of endothelioma of the brain. The upper two thirds of the left kidney were replaced by a Grawitz tumor. Section showed a partially encapsulated nodule, compressing the adjacent kidney tissue. The capsule contained blood and pigment. The nodule consisted of solid sheets of foamy cells arranged in columns with a fine stroma of connective tissue and capillaries. Considerable pigment was present. The cytoplasm in places was clear, and in other places had a more definite honeycomb appearance. The nuclei were more or less regular in size, with slight variations. The resemblance to the fascicular layer of the suprarenal cortex in one area was extremely suggestive.

This was a hypernephroma showing the malignant transformation of a benign tumor arising from the cortical suprarenal tissue in the kidney.

CASE 42.—L. C., a man, died of generalized arteriosclerosis and hypertension. There was a tumor 7 by 5 by 5 cm. in the left kidney.

On section, the tumor was composed of masses of fairly uniform polyhedral cells arranged in a continuous mosaic. The cytoplasm was foamy; the nuclei were small and eccentric. Between every two or three columns of cells there were fine septums containing capillaries. This portion of the tumor was perfectly uniform and benign, having a resemblance to the fascicular layer of the cortex of the supra-

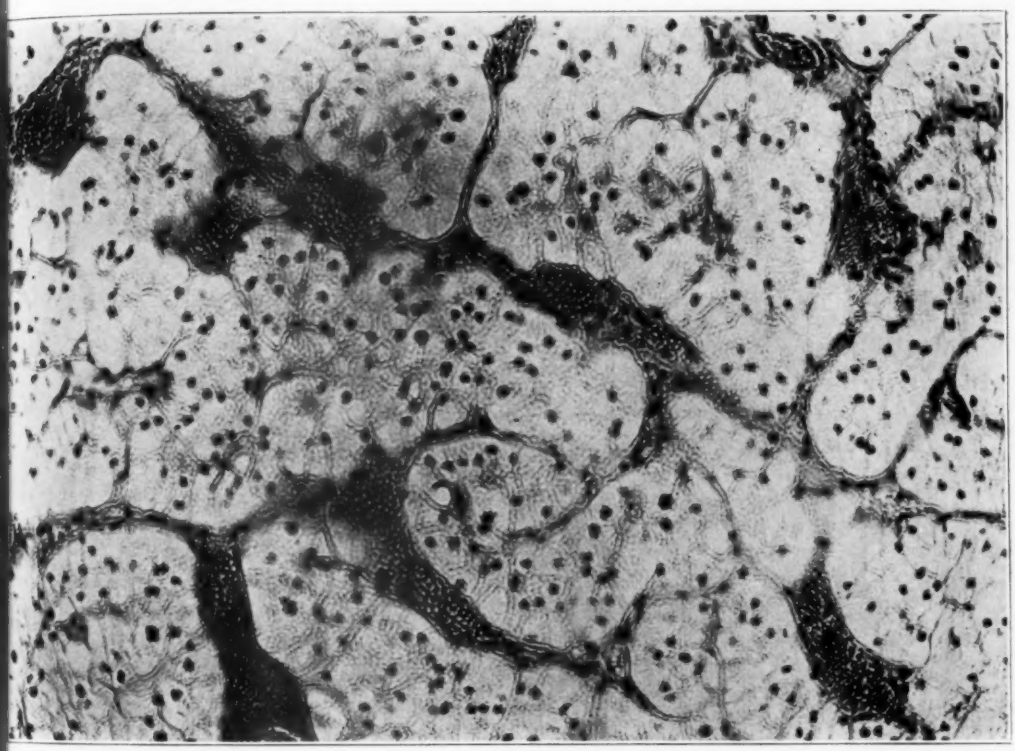

Fig. 19 (case 42).—Benign appearance of the hypernephroma cells. Note the uniformity in size of the nuclei, the honeycomb structure of the cytoplasm and the mosaic arrangement of the cells. Reduced from a magnification of × 240.

renal gland. Other sections of the tumor showed the structure typical of a malignant hypernephroma with cyst formation, hemorrhage and necrosis. There was marked pleomorphism of the cells and nuclear elements, and in some areas the cells lay singly and were extremely large. Giant cells with large irregular nuclei were present.

This was a striking instance of the transition of a benign growth into a malignant one. A section from one or two areas of the tumor would have failed to reveal the striking malignant character of the growth (figs. 19 and 20).

Case 43.—M. L., a man, aged 70, died of carcinoma of the esophagus. There was a pea-sized nodule in the left kidney.

On section, the nodule was small and encapsulated, and it compressed the surrounding tissue. It was composed of polyhedral cells arranged in irregular columns and lying in a network of thin connective tissue containing capillaries. The cytoplasm was honeycombed. In places small lumina had a pseudo-alveolar formation. In other areas, a typical hypernephroma was seen. The central portion of the nodule contained large quantities of blood, which lay in cystlike spaces. In other places, definite glandlike structures were distended with blood and were lined

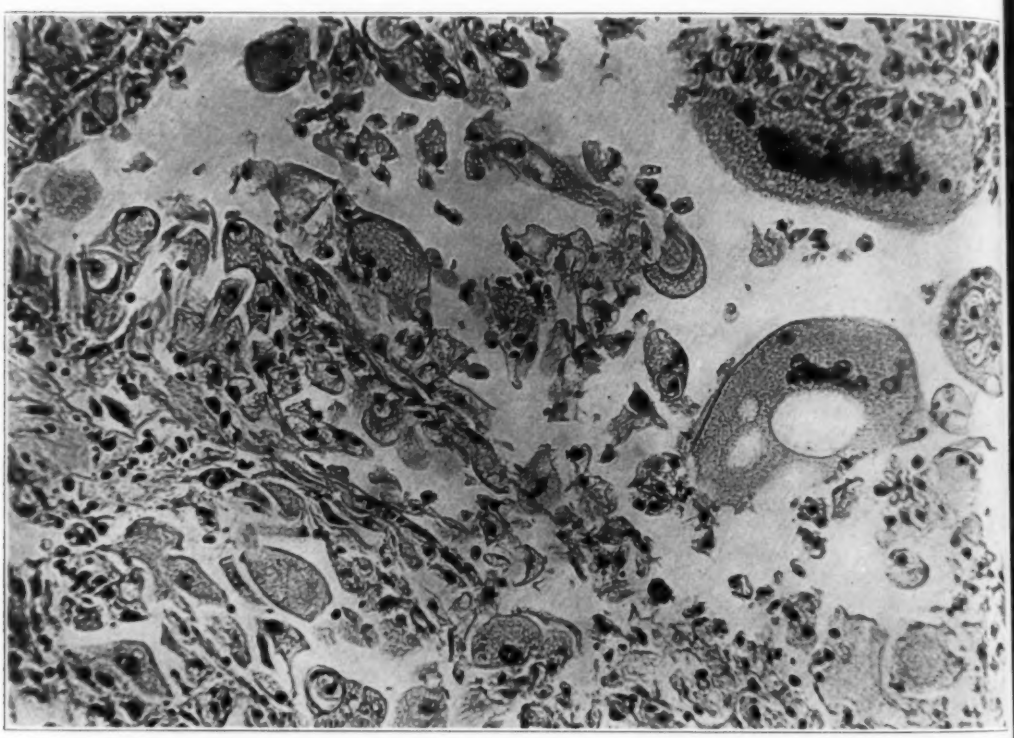

Fig. 20 (case 42).—Section showing marked pleomorphism of the tumor cells with evidence of papillary structure and giant cell formation. Reduced from a magnification of × 240.

by clear, vacuolated, cuboidal, polyhedral cells. This was a typical benign hypernephroma.

Case 44.[16]—M. F., a man, aged 24, died of uremia and hypertension. At autopsy, a large tumor of the suprarenal gland was found.

The tumor consisted of columns and masses of polyhedral cells closely packed and lying in an irregular stroma of connective tissue. The cells showed marked pleomorphism. There was a tendency toward alveolar formation and the develop-

16. This case was reported by Dr. B. S. Oppenheimer and Dr. A. Fishberg.

ment of papillae. In other areas, the tumor resembled the cortex of the suprarenal gland. Necrosis and hemorrhage were present. The left suprarenal gland contained ten benign adenomas.

The diagnosis was hypernephroma of the suprarenal gland arising from a benign adenoma. The relation between benign and malignant hypernephroma was strikingly illustrated.

PATHOGENIC GAS-PRODUCING ANAEROBIC BACILLI IN CHRONIC ULCERS*

MELVILLE H. MANSON, M.D.
MINNEAPOLIS

Report of Cases
  Summary of Cases
Suggested Relationship Between Chronic Ulcers and Gas Gangrene
Technic
  Isolation of Anaerobes
  Pathogenicity
  Differentiation of Organisms
  Clinical Application
Results
  Cases Harboring Anaerobes
  Control Cultures
Ubiquity of Clostridium Welchii
Comment
  Significance of Results
  Status of Anaerobic Antitoxins
Summary

Two virulent cases of gas gangrene following amputation of extremities that were the site of chronic ulcers stimulated interest in this subject. Gas gangrene is usually the result of severe trauma with muscle destruction and a wound grossly contaminated with dirt and foreign bodies. The problem presented itself as to the origin of the gas bacillus infection in postoperative wounds, in which all the usual aseptic and antiseptic precautions had been employed, and the possible relationship of the ulcers to the development of the gas bacillus infection was suggested. This paper includes a report of two cases and a bacteriologic study of chronic ulcerating lesions with particular reference to the occurrence of the pathogenic, gas-producing anaerobes.

REPORT OF CASES

CASE 1.—G. K., aged 43, a barber, was admitted to the University Hospital on Sept. 30, 1929. He had a history of diabetes dating back to 1917, twelve years prior to admission, for which he had taken no treatment. In August, 1929, he noted a small scab on the anterior tibial aspect of his left leg, which increased in

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* From the Department of Surgery of the University of Minnesota.

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size and became quite painful. Local treatment was instituted, but the ulcer increased in size and at the time of admission measured about 5 cm. in diameter. There was considerable infection present, the area surrounding the lesion being reddened, edematous and indurated. The patient was placed on a basal maintenance diet, and conservative treatment was directed to the ulcer.

Roentgen examination of the left leg showed calcified thrombi in the veins. There was a distinct destructive process in the cortex of the anterior surface of the tibia with little or no new bone formation. The appearance was characteristic of secondary invasion of the bone with a soft tissue infection that was producing considerable bone destruction. There was no evidence of gas in the soft tissues.

Amputation was advised, but the patient refused. Conservative local measures consisting of elevation of the extremity, application of packs saturated with surgical solution of chlorinated soda (Dakin's solution) and heat were continued, together with careful dietary regulation for the diabetes.

On October 25, as the ulcer had shown no evidence of improvement and was causing the patient considerable pain, he consented to amputation, qualifying his consent, however, to the extent that the amputation be done below the knee. Because of the close proximity of the ulcer to a satisfactory amputation level and the presence of the diabetes, he was advised that an amputation through the lower thigh would be a safer procedure. This opinion was not shared by the patient.

The lesion was covered with sterile dressings, the leg prepared by cleansing with benzine and ether, application of two coats of 3.5 per cent alcoholic iodine solution which, after drying, was removed with Richardson's [1] solution. Under spinal anesthesia, the leg was amputated about 5 cm. below the tibial tubercle. A tourniquet was used on the thigh and was left on for not more than five minutes. Bleeding was apparently free on its removal; the muscles appeared normal, and the flaps were closed over a split Penrose drain.

The immediate postoperative course was very satisfactory. The stump was dressed the following day and appeared in healthy condition. On the evening of the third day, the patient complained of considerable pain in the stump. His temperature was elevated to 102.6 from 99 F. The dressings were removed, and the characteristic odor of gas gangrene was immediately noted. There were several copper-colored blebs present; the edges of the flaps were of a gunmetal blue and gas was palpable, especially on the medial aspect to the junction of the lower and middle thirds of the thigh. Roentgen examination showed a large amount of gas in the soft tissues about the stump, extending well up along the shaft of the femur to about 10 cm. above the knee joint (fig. 1).

Under spinal anesthesia, a quick amputation through the upper thigh was done by the transfixion method. All of the muscles except the gracilis appeared normal in color, reacted to stimulation and bled freely. The gracilis was dissected upward until it was no longer brownish and contracted when stimulated. The flaps were not closed. Prior to the operation, 20 cc. of Bacillus perfringens antitoxin was given intramuscularly; 150 cc. was injected into the stump at the time of the operation.

The patient's condition was critical the next morning, and 20 cc. of Bacillus perfringens antitoxin was given intravenously, together with physiologic solution

1. This is the routine skin preparation at the University Hospital. Sodium thiosulphate neutralizes the iodine and removes the iodine stain much more efficiently than does alcohol alone. This technic was introduced nine years ago by Dr. Fred Richardson, of Minneapolis, then an intern at the hospital.

of sodium chloride. There was considerable abdominal distention; the blood sugar, which had been 150 mg., rose to 600 mg. The pulse became rapid and thready about noon the day following operation, and death occurred.

Postmortem examination showed the amputation stump to be clean. There was no discoloration, no odor and no crepitation. The subcutaneous fat was about 10 cm. in thickness, and there was an enormous amount of fat in the peritoneal cavity. There was a marked sclerosis of the coronary arteries, especially the left branch. The lumen was pinpoint in size, and in the same region myocardial

Fig. 1 (case 1).—Roentgenogram taken immediately prior to secondary amputation. Diffuse mottling of soft tissues with gas extending upward on lateral sides above knee joint is shown.

fibrosis was seen. No gas was found in the blood vessels or in the liver. There were a chronic cholecystitis and cholelithiasis, cloudy swelling of the kidney and liver and a healed miliary tuberculosis of the pleura, spleen, kidney and liver.

Case 2.—H. W., a man, aged 55, was admitted to the hospital on Sept. 17, 1929, and died on Feb. 18, 1930. He was undernourished and prematurely senile, and entered the hospital with a chief complaint of an ulcer on the left heel. The immediate history preceding the onset of the ulcer was that in December, 1928, the patient experienced what he termed chilblains of both feet, more marked

on the left than on the right. The left heel cracked at the site of a callus, and a sore developed underneath, which was opened. In August, 1929, the lesion was excised and curetted down to the bone, following which healing did not occur. The patient's history showed that he had had syphilis, the onset of which was twenty years prior to admission. He had had several courses of treatment, the last ending in August, 1929.

Examination showed a deep, indurated ulcer on the left heel, from which exuded considerable purulent discharge. Treatment consisted of irrigations with

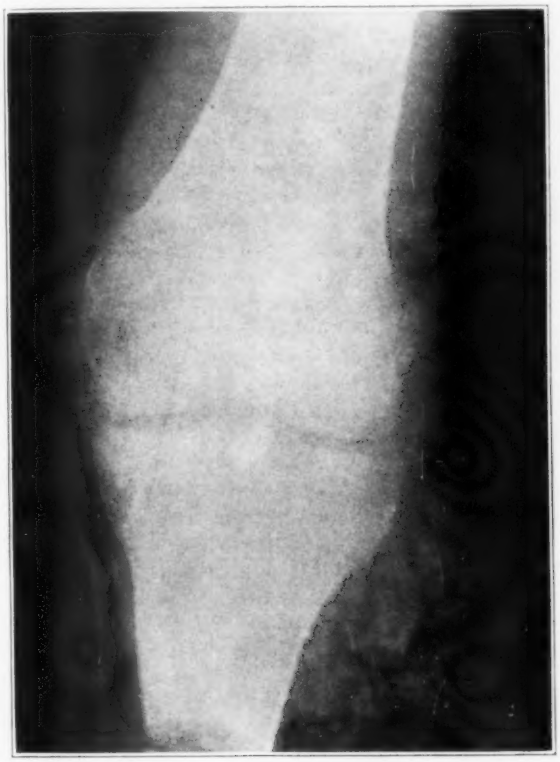

Fig. 2 (case 2).—Roentgenogram taken immediately prior to secondary amputation. Bubbles of gas are seen throughout the soft tissues extending upward along the femur.

surgical solution of chlorinated soda, elevation and heat. There was no response to conservative treatment, and on October 11 the ulcer was excised, following which the wound was treated with packs saturated in surgical solution of chlorinated soda. By November 4, the granulations appeared quite healthy, and the transfer of a pedicle flap from the calf of the right leg was contemplated. This flap was outlined and raised and resutured to its bed preparatory to a transfer. The lower portion of the ulcer was excised. The exposed bone was removed with a chisel and the curet, leaving a free bleeding raw surface. The ulcer, however, failed to granulate, and this plan was abandoned. Further antisyphilitic treatment

was instituted. During this course of treatment, the patient complained considerably of severe pain in the foot, was unable to sleep at night and required considerable narcotics for relief. Circulatory tests of the lower extremity showed an oscillometric index with the Paschon oscillometer of a half above the right ankle, zero above the left ankle, one and one-half above the left knee and from six to seven oscillations above the right knee.

The pain that the patient was experiencing was attributed to the circulatory inadequacy, and because of the extreme pain and the election on the part of the patient, an amputation was done on January 23 under spinal anesthesia, the left leg being amputated about 8 cm. below the tibial tuberosity. Preparation of the skin was the same as in the preceding case. On the morning of the third postoperative day, a definite odor of gangrene was noted about the stump, and on examination there were several discolored brownish blebs. The distal end of the stump appeared rather purplish, and on palpation definite crepitation could be felt, most marked on the medial aspect of the thigh as high as about the middle of the stump. Clostridium welchii was identified in the exudate (fig. 2).

On January 25, an amputation through the middle thigh was done under spinal anesthesia. Prior to amputation, 30 cc. of Bacillus perfringens antitoxin was given intravenously and 150 cc. injected into the stump. The stump was left open, and subsequent treatment consisted of irrigations with surgical solution of chlorinated soda. Later, the same day, 100 cc. of Bacillus perfringens antitoxin was given intramuscularly; on January 29, 20 cc. was given intramuscularly.

The postoperative course was uneventful until the ninth day, when a rather severe secondary hemorrhage occurred. The entire stump was opened, the hemorrhage controlled, and the patient given a transfusion with 600 cc. of whole blood. No further evidence of gas gangrene manifested itself. The patient's subsequent course, however, was complicated by the fact that he had urethral strictures, which, following the postoperative catheterization, totally obstructed the urethra. A ureteral catheter was used for drainage, and infection developed. A suprapubic cystotomy was done. Subsequently, bronchopneumonia developed, and the patient died on Feb. 18, 1930.

Postmortem examination showed no evidence of gas gangrene. There was bilateral bronchopneumonia and marked infection of the entire urinary tract.

Summary of Cases.—The case histories of two patients presenting chronic ulcers necessitating surgical intervention because of their resistance to conservative treatment are reviewed. In one patient, who had diabetes, the ulcer and the concomitant infection had a reciprocal deleterious influence on the diabetes. The other patient had syphilis and suffered from a painful ulcer on the heel. Amputation of the ulcer-bearing extremity below the knee was done in both instances. The disability from pain was great in both cases. On the third postoperative day, gas gangrene developed in the amputation stumps. There was no evidence of, or reason to suspect, gas bacillus infection in the ulcers prior to operation.

SUGGESTED RELATIONSHIP BETWEEN CHRONIC ULCERS AND GAS GANGRENE

Because of the similarity of the two cases and the fact that no other cases of gas bacillus infection developed in patients who were operated

on at the same time, it appeared likely that the source of the infection may have been the chronic ulcers. No reference has been found in the literature regarding the development of gas gangrene in a chronic ulcer, although several cases of tetanus in which an ulcer was the portal of entry have been reported (Andrews and Horder,[2] Schmüziger,[3] DaCosta[4]). The possibility of contamination from the skin or from the catgut employed is unlikely. This will be discussed more fully under comment. The logical premise to determine this suggested relationship would be the frequency with which chronic ulcers harbor pathogenic anaerobes. Consequently, cultures were made of this type of lesion from patients being treated in the dispensaries or wards of the University Hospital.

TECHNIC

Isolation of Anaerobes.—Material to be cultured was obtained on a sterile applicator and placed in a sterile glass test tube. The swab was then transferred to liver peptone or dextrose brain-broth medium. This had been boiled for fifteen or twenty minutes and cooled immediately prior to its use. After incubation for from twenty-four to forty-eight hours, the culture was usually examined for the presence or absence of spores. If spores were present, the culture was heated to 80 C. for fifteen or twenty minutes to kill the nonspore-forming rods and cocci that were usually present. The culture was then plated anaerobically on Adams'[5] dextrose sodium sulphite, ferric chloride agar and incubated for twenty-four or forty-eight hours. This medium was freshly made before each plating by adding to a tube of dextrose agar 1 cc. of sodium sulphite solution (20 Gm. anhydrous salt to 100 cc. of water) and 0.1 cc. of ferric chloride solution.

Anaerobic growth is indicated on this medium by the appearance of typical black colonies. Single colonies were picked and planted into deep shake-agar tubes, milk and liver peptone, or brain-broth medium. The brain-broth was used exclusively in the latter part of this study. The stormy fermentation in milk, produced by a gram-positive, nonmotile anaerobic bacillus, was considered characteristic of Clostridium welchii. It was found later that purification was rendered somewhat easier by utilizing the fact that Clostridium welchii reproduces at a much earlier period than most other organisms. That is, in a favorable medium containing fermentable sugar, as the dextrose brain medium, Clostridium welchii will attain vigorous gas production in three or four hours, while stapylococci, streptococci and the gram-negative rods will either not be in evidence, or be in an exceeding minority. Thus,

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3. Schmüziger, P.: Ein Fall von Tetanus mti Ulcus curis als Eingangspfort, Deutsche Ztschr. f. Chir. **188**:161, 1924.

4. DaCosta, J. C.: Modern Surgery, ed. 10, Philadelphia, W. B. Saunders, 1931, p. 136.

5. Adams, B. A.: The Enumeration of the Anaerobic Sulphite Reducing Bacteria and the Significance of Their Presence in Water, Water and Water Engineering, Sept. 20, 1929.

by transferring the culture into fresh medium every three or four hours, the Welch bacillus may be isolated from the less rapidly reproducing organisms in the course of about two days.

Pathogenicity.—Inoculation of from 0.5 to 1 cc. of a twenty-four hour culture in guinea-pigs was made in every case in which a gram-positive anaerobe was isolated. The hair was clipped, the skin prepared with tincture of iodine and the culture injected intramuscularly into the thigh. A typical reaction in a guinea-pig consists of an edema which progresses rapidly, with gas formation that is palpable within two or three hours. The skin may exude serum or may slough, and death occurs in from eight to twenty-four hours if the culture is virulent. In some cases a spontaneous perforation occurred, in which event recovery not infrequently ensued (figs. 3 and 4).

Fig. 3.—Guinea-pig two weeks after inoculation of culture from case 7 into the right thigh. The large gangrenous area later sloughed off and healing resulted.

Differentiation of Organisms.—Gram-positive anaerobes, other than Clostridium welchii, were differentiated by the most prominent cultural and morphologic characteristics in which they differ from the Welch bacillus. Differentiation between Clostridium edematis-maligni (vibrion septique) and Clostridium welchii was based on the fact that the former is somewhat more slender and is motile, whereas the latter is short, stubby and nonmotile. Cultures of edematis-maligni in milk produce acid and clotting. This occurs at a later period and is distinctly a different reaction from the stormy gas fermentation that is evoked by the Welch bacillus.

Sporogenes is also a motile organism, and is easily differentiated from Clostridium welchii in that it is strongly proteolytic, and the reaction resulting from its activity is alkaline rather than acid. The proteolysis is recognized by the

blackening of the brain in a broth culture, due to the formation of sulphides. A putrid odor results from this action which is very offensive.

Bacillus subtilis, megatherium and related organisms are morphologically very similar to Clostridium welchii but are easily differentiated by their profuse aerobic growth characteristics.

Technic for Clinical Application.—It is apparent that the technic as described is too lengthy and detailed to be of value if one wishes only to determine whether or not the Welch bacillus is present in any lesion. Any "short cut" method in bacteriology is apt to result in unreliable results and, in general, is not to be encouraged. However, the milk reaction to the growth of Clostridium welchii is a phenomenon sufficiently characteristic to warrant its use as a diagnostic procedure. This stormy fermentation has been used as a criterion for the presence of Bacillus welchii by Glynn,[6] Hewes and Kendall,[7] Orton,[8] Rettger,[9] Simonds [10] and others.

Fig. 4.—Same guinea-pig as shown in figure 3. The perforation is seen leading to a necrotic cavity which previously contained gas and sanguineous fluid. The perforation occurred about thirty hours after the injection of the culture.

The method consists simply of boiling a tube of fresh milk—whole milk is preferable—for from twenty to thirty minutes immediately prior to its use. This is

6. Glynn, E. E.: The Relation Between Bacillus Enteritidis Sporogenes of Klein and Diarrhea, Thompson Yates Lab. Rep. **3**:131, 1900-1901.

7. Hewes, H. F., and Kendall, A. I.: The Gas Bacillus as an Agent of Intestinal Fermentation and Diarrhea, Boston M. & S. J. **166**:75, 1912.

8. Orton, S. T.: A Note on the Occurrence of B. Aerogenes Capsulatus in an Epidemic of Dysentery and in the Normal, J. M. Research **29**:287, 1913-1914.

9. Rettger, L. F.: Studies on Putrefaction, J. Biol. Chem. **2**:71, 1906.

10. Simonds, J. P.: Studies in B. Welchii with Special Reference to Classification and to Its Relation to Diarrhea, New York, Rockefeller Institute for Medical Research, 1915, no. 5.

cooled rapidly. A swab from the suspected lesion is introduced, and the culture placed in an incubator at 37.5 C. If the Welch bacillus is present, gas bubbles may be seen rising to the surface within two or three hours, and within a period of six or eight hours the whole content will be involved by the rigorous gas production. At the end of twenty-four hours the milk is separated into a clean whey, and the clot is torn and fragmented throughout the tube.

The question may arise as to the least number of spores or organisms necessary to produce this reaction, for if it is not selective enough, some lesions containing only a few organisms might be considered negative. Simonds [10] found that dilutions that yielded two or three colonies when planted on anaerobic agar plates invariably gave positive reactions in milk. In most instances in which there was but one colony on a plate, there was a positive milk reaction. Thus it is seen that the method is sufficiently selective to be of definite value, and because of its simplicity should be used more extensively.

RESULTS

Culture of thirty-two chronic ulcerating lesions revealed that eleven, or 34.37 per cent, were harboring pathogenic, gas-producing anaerobes. Clostridium welchii was present in each of the eleven positive cultures, associated with Clostridium edematis-maligni (vibrion septique) in two instances. Clostridium tetani was isolated in one case. In two instances (cases 7 and 10), the Welch bacillus was isolated on repeated occasions. The cultures of sporogenes were not pathogenic for guinea-pigs. The organisms designated in the table as facultative will be discussed in more detail in the control series. Only the bacilli that were pathogenic for guinea-pigs are controlled Clostridium welchii in this series. The table on the next page indicates the type of lesions cultured.

Analysis of the results with regard to sex or age shows no significant findings. The duration of the varicose ulcers from which the anaerobes were isolated averaged approximately six years longer than that of the ones that yielded no anaerobes. This does not include the case of forty-five years' duration. Whether the longer duration was due to the presence of the anaerobes is difficult to determine. The appearance of the ulcers that contained the anaerobes was of no apparent significance, and none of them developed any evidence of gas bacillus infection. The environment of the patients as determined by their occupation was not analyzed in detail. It has been suggested that those who are in closer contact with the soil, as farmers, might harbor this group of organisms more often than people employed in other occupations. The patient from whom Clostridium tetani and Clostridium welchii were obtained was a farmer (case 3). Case 21, from which Clostridium edematismaligni and Clostridium welchii were both isolated, was also that of a farmer. None of the other patients were employed in the country at the time the positive cultures were obtained.

Types of Lesions Cultured *

Patient	Sex	Age	Lesion	Duration	Culture
1. A. J.	F	27	Ulcer at site of toe amputation.....	2 yrs.	No anaerobic growth
2. M. L.	M	76	Ulcer at site of thigh amputation..	6 yrs.	No anaerobic growth
3. C. M.	M	47	Trophic ulcer of heel.....	2 yrs.	Clostridium tetani and Clostridium welchii
4. W. B.	M	31	Varicose ulcer, left leg.....	8 yrs.	Clostridium welchii
5. L. C.	F	38	Varicose ulcer, right leg.....	2 yrs.	No anaerobic growth
6. C. L.	F	68	Varicose ulcer, left leg.....	4-5 yrs.	No anaerobic growth
7. A. H.	F	66	Varicose ulcer, left leg.....	16 yrs.	Clostridium welchii
8. W. C.	M	38	Varicose ulcer, left leg.....	2 yrs.	No anaerobic growth
9. L. F.	M	59	Epithelioma, hand	?	No anaerobic growth
10. T. S.	M	60	Varicose ulcer, left leg.....	10-15 yrs.	No anaerobic growth
			Varicose ulcer, right leg.....	4-5 yrs.	Clostridium welchii
11. E. J.	F	60	Varicose ulcer, left leg.....	?	No anaerobic growth
12. M. Y.	G	20	Ulcer following trauma.....	1 mo.	Facultative anaerobic growth
13. J. M.	M	47	Ulcer following vein injection.....	14 days	Facultative anaerobic growth
14. J. G.	M	54	Varicose ulcer	12 yrs.	Clostridium welchii
15. A. S.	F	46	Varicose ulcer, right leg.....	3 yrs.	No anaerobic growth
16. I. C.	F	34	Varicose ulcer, right leg.....	1-2 yrs.	No anaerobic growth
17. G. E.	F	22	Ulcerating erythema induratum....	6 mos.	Sporogenes and Clostridium welchii
18. J. E.	M	55	Sacral decubitus ulcers.....	10 days	Sporogenes
19. M. S.	F	64	Sacral decubitus ulcers.....	14 days	Clostridium welchii and Clostridium edematis maligni
20. C. M.	M	26	Sacral decubitus ulcers.....	10 days	Sporogenes
21. V. W.	M	51	Chronic ulcer, heel.....	5 yrs.	Clostridium welchii and Clostridium edematis maligni
22. E. E.	M	25	Ulcer, dorsum of hand.....	6 mos.	No anaerobic growth
23. W. H.	M	60	Varicose ulcer	45 yrs.	Clostridium welchii
24. J. S.	F	52	Varicose ulcer, right leg.....	7 yrs.	Facultative anaerobic growth
25. G. N.	M	61	Syphilitic ulcer, right leg.....	5 yrs.	Facultative anaerobic growth
26. F. T.	M	12	Trophic ulcer, foot; spina bifida...	6 yrs.	Facultative anaerobic growth
27. O. K.	M	47	Ulcer over left tibia; osteomyelitis.	6½ yrs.	Facultative anaerobic growth
28. B. K.	F	54	Sacral decubitus ulcer.....	.....	Clostridium welchii
29. J. N.	F	27	Varicose ulcer, right leg.....	7 mos.	No anaerobic growth
30. P. B.	M	60	Ulcerating carcinoma of back.....	12 yrs.	No anaerobic growth
31. J. P.	F	38	Sacral decubitus ulcers.....	.....	Clostridium welchii
32. I. E.	F	52	Varicose ulcer, right leg; purulent discharge	4-5 yrs.	No anaerobic growth

Summary

	Total	Harboring Anaerobes
Varicose ulcers	14	5
Decubitus ulcers	5	3
Miscellaneous ulcers	13	3

	Years
Average age of patients from whom anaerobic cultures were obtained.....	50
Average age of patients from whom no anaerobic cultures were obtained.....	43
Average duration of varicose ulcers harboring anaerobes	17+
Average duration of varicose ulcers minus the case of forty-five years' duration...	10+
Average duration of varicose ulcers harboring no anaerobes.....	4+

	Males	Females
Whole group	17	15
Positive culture group.....	6	5

* All of the lesions showed a variable flora of aerobic bacteria including staphylococci, streptococci, B. coli, gram-positive diplococci and gram-positive and gram-negative bacilli.

Cases Harboring Anaerobes.—CASE 3.—C. M., a farmer, aged 47, presented a deep penetrating ulcer of the left heel. The lesion was traumatic in origin due to anesthesia of the heel following a sural nerve injury. Cultures taken in June showed Clostridium tetani, producing typical tetanus in a guinea-pig. Cultures taken in September, in an effort to recover tetanus again, revealed Clostridium welchii. The patient has not shown symptoms of infection with either organism at any time (fig. 6).

CASE 4.—W. B., a man, aged 31, presented a large varicose ulcer on the medial aspect of the left leg which had been present for eight years. No surgical treatment was instituted. Cultures were positive for Clostridium welchii.

Fig. 5 (case 7).—Ulcer that repeatedly yielded Clostridium welchii. At no time was there evidence of gas bacillus infection.

CASE 7.—A. H., a housewife, aged 66, presented a varicose ulcer of sixteen years' duration, on the anterior tibial aspect of the left leg. Injection treatment for the varicosities had been in effect for two months before any cultures were taken. Cultures repeatedly showed Clostridium welchii. On one occasion a high degree of virulence for guinea-pigs was shown. A lethal outcome occurred in from six to eight hours after intramuscular injection. Two weeks later, the virulence was apparently attenuated. The guinea-pig lesion perforated spontaneously, and recovery ensued (fig. 5).

CASE 10.—T. S., a man, aged 60, is being treated in the outpatient department for bilateral varicose ulcers of the legs. Cultures from the ulcers on the right leg have shown Bacillus welchii on repeated occasions for a period of two months. No positive cultures were obtained from a large ulcer on the left leg. This may indicate that the positive cultures from the ulcer on the right leg are more than a casual finding, i. e., some factors may be present in this ulcer that are not present in the other lesion, permitting the harboring of the anaerobes.

CASE 14.—J. G., a man, aged 54, had been seen at intervals for over five years, during which time he received injection treatments for varicose veins. On the medial aspect of the lower part of the left leg there was an ulcer of twelve years' duration. The surrounding skin was marked by discoloration and suffered nutritional changes. The Welch bacillus obtained in this case killed a guinea-pig in ten hours.

Fig. 6 (case 3).—This lesion was of two years' duration. Cultures on one occasion showed Clostridium tetani. Three months later Clostridium welchii was recovered from the ulcer. No evidence of either tetanus or gas bacillus infection developed.

CASE 17.—G. E., a woman, aged 22, had multiple ulcerating lesions on her extremities, the etiologic factor being erythema induratum. Cultures showed Clostridium welchii and sporogenes. No gas gangrene was ever apparent.

CASE 19.—M. S., a woman, aged 64, had senile dementia and hemiplegia. She had a large sacral decubitus ulcer which yielded a pathogenic, gas-producing anaerobe, identified as Clostridium welchii, and a strain of Clostridium edematis-maligni.

CASE 21.—V. W., a farmer, aged 51, sustained an injury to his heel five years prior to admission, which resulted in an ulcer. The lesion had alternately been open and healed several times in the interim. Cultures showed Clostridium

welchii and Clostridium edematis-maligni (vibrion septique). This lesion was treated with surgical solution of chlorinated soda by means of packs and irrigations, subsequently excision and skin grafting were performed.

CASE 23.—W. H., a man, aged 60, had a varicose ulcer on the medial aspect of his right leg for forty-five years. There was a marked nutritional change in the surrounding tissues. Cultures showed the bacillus of Welch and streptococci. His veins were being treated by the injection method.

CASE 28.—B. K., a housewife, aged 54, was admitted to the hospital because of a fractured femur. She also had diabetes. A plaster cast was applied, and later a pressure sore developed over the sacral region. Cultures showed Clostridium welchii and staphylococci.

CASE 31.—J. P., a housewife, aged 38, developed a transverse myelitis in the lower thoracic segment of the spinal cord with paralysis of both lower extremities, incontinence and anesthesia. A large sacral ulcer developed from which cultures showed Clostridium welchii together with staphylococci and gram-negative bacilli.

Control Cultures.—Cultures were made from the intact normal skin of fifty-two persons to determine whether or not the incidence of pathogenic anaerobic gas-producing bacilli was any greater in ulcerating lesions than on normal skin. Forty-six cultures were taken from the legs of patients presenting themselves to the admitting dispensary of the University Hospital. Four cultures were obtained from the legs of medical students and two from staff physicians.

Aerobic, motile gram-positive bacilli were obtained in every instance. These organisms were not completely identified, as they differed from B. subtilis and B. megatherium in minor cultural characteristics, but they undoubtedly belong to this group of bacilli. Five guinea-pigs were given intramuscular injections of cultures of these motile, aerobic spore-forming rods, and in each instance the organisms were nonpathogenic. A number of these cultures exhibited some anaerobic growth, with no gas formation, and it is this type of organisms that is designated as facultative in the table. There are ninety-three organisms of this genus classified in Bergey's[11] "Manual of Determinative Bacteriology," and probably many others which have not been completely identified.

Seven of the control cultures contained nonmotile bacilli, and also exhibited anaerobic growth. Four of these showed gas formation in deep dextrose agar and produced stormy fermentation in milk. One cubic centimeter of the broth culture of each of the seven nonmotile organisms was injected intramuscularly into guinea-pigs. Three of these animals survived with no demonstrable lesion being produced.

Of the four animals given injections with the cultures that produced stormy fermentation in milk, two showed evidence of gas formation and

11. Bergey, David H.: Manual of Determinative Bacteriology, ed. 3, Baltimore, Williams & Wilkins Company, 1930, p. 430.

edema. One of these died within forty-eight hours; the other survived with no necrosis or ulceration. The patients from whom these two cultures were obtained were both housewives residing in the city (dispensary nos. 599309 and 596769). The two remaining animals died, three and four days following injection, but neither showed evidence of gas bacillus infection. Unfortunately these two guinea-pigs were extremely emaciated and unsuitable for experimental purposes, but were used, of necessity, as no others were available. It is impossible to state whether or not these organisms were pathogenic, but as the cultural characteristics were those of Clostridium welchii, they are included as positive cultures. One of the patients from whom these cultures were obtained was a waitress, the other a mechanic (dispensary nos. 599367 and 599349, respectively). Thus, from the fifty-two cultures of normal skin there were four (7.67 per cent) in which Clostridium welchii was present.

UBIQUITY OF CLOSTRIDIUM WELCHII

It will be noted that the terms Clostridium welchii, B. aerogenes-capsulatus, B. perfringens and the Welch bacillus, are all used in this paper to designate the same organism. The term Clostridium is applied to the genus of spore-bearing anaerobes of the family of Bacillaceae (Bergey).

The organism known as Clostridium welchii was described by Welch[12] in 1892, under the name of B. aerogenes-capsulatus. The name B. welchii was suggested by Migula (1900). The same organism was described and called B. phlegmonis-emphysematosae by Eugene Fraenkel (1893), B. perfringens by Veillon and Zuber (1898) and B. saccharobutyricus-immobilis by Schattenfroh and Grassberger (1900). Although all of the synonyms are found in the literature, the terminology accepted by American bacteriologists is Clostridium welchii (Bergey).

Clostridium welchii is found in the gastro-intestinal tract of man and of practically all animals, both herbivorous and carnivorous. It is found extensively in soil and constantly in sewage. Members of this group have been isolated from gallstones, bile (Dayton, Gilbert and Lippmann,[13] Williams[14]), shot-gun wads, woolen clothing and blankets

12. Welch, W. W., and Nuttall, G.: A Gas-Producing Bacillus (B. Aerogenes Capsulatus) Capable of Rapid Development in the Blood Vessels After Death, Bull. Johns Hopkins Hosp. **3**:1 (July) 1892.

13. Gilbert, A., and Lippmann, A.: Le microbisme biliare normal, Compt. rend. Soc. de biol. **55**:157, 1903.

14. Williams, P. F.: A Bacteriologic Study of the Human Bile, New York State J. Med. **93**:934 (May) 1911.

(Gage,[15] Fleming[16]). Of particular interest is Meleney's[17] report of finding 38 instances of pathogenic, gas-producing anaerobes in 83 cultures made of raw surgical catgut. Numerous observations made during the World War were to the effect that the Welch bacillus was frequently found in wounds in which there was no evidence of gas gangrene. Of 890 wounds studied at Evacuation Hospital no. 8, A. E. F., 478, or 53 per cent, contained anaerobic bacilli of the Welch group. Of these, 321, or 67 per cent, at no time showed evidence of gas gangrene.[18]

Raymond and Veight,[19] studying the bacterial flora of war wounds, examined the surface exudate in 137 consecutive cases and found Clostridium welchii present in 23 per cent. Definite gas infection was present in 2.9 per cent, and 5.1 per cent if the doubtful cases were added. Of the cases in which Clostridium welchii was found on culture, there was definite gas infection in 13 per cent, adding the doubtful cases, the percentage was 22.5 per cent.

Stoddard[20] stated that studies by Fleming in 1914-1915 showed the presence of Clostridium welchii in 81 per cent of 127 wounds from one to seven days old, in 34 per cent of 56 wounds of eight to twenty-one days and 18.5 per cent of wounds more than twenty-one days old. The same author stated that Plisson found a harmless persistence of Clostridium welchii until the tenth day in 22 of 180 cases.

Tulloch,[21] who made a detailed study of war wounds for the British Committee on anaerobic wound infections, found "light anaerobic infection in fourteen instances, no anaerobic infection in twenty-nine instances" in forty-three wounds in which delayed healing occurred. In another series of cases in which swabs were taken seven days before the wounds had healed sufficiently for the patient to be

15. Gage, F. M.: Gas Bacillus Infection—A Frequently Unnoticed Source in Civil Life, Am. J. Surg. **1**:177 (Oct.) 1926.

16. Fleming, Alexander: Some Notes on the Bacteriology of Gas Gangrene, Lancet **2**:376 (Aug. 7) 1915.

17. Meleney, F. L., and Chatfield, Mabel: How Can We Insure the Sterility of Catgut? Surg., Gynec. & Obst. **50**:271 (Jan.) 1930; Sterility of Catgut in Relation to Hospital Infections, ibid. **52**:430 (Feb.) 1931.

18. Callender, G. R., and Coupal, J. F.: Pathology of Gas Gangrene Following War Wounds, in Medical Department of United States Army in the World War, Washington, D. C., Government Printing Office, 1929, vol. 12, sect. 2.

19. Raymond and Veight: Bacterial Flora of War Wounds, Bull. et mém. Soc. méd. d. hôp. de Paris **41**:1302, 1917.

20. Stoddard, James L.: The Occurrence and Significance of B. Welchii in Certain Wounds, J. A. M. A. **71**:1400 (Oct. 26) 1918.

21. Tulloch, W. J.: Report of Bacteriological Investigation of Tetanus Carried Out on Behalf of the War Office Committee for the Study of Tetanus, J. Hyg. **18**:104 (Aug.) 1919.

considered convalescent, the following results were obtained: (*a*) no anaerobes in nineteen instances, (*b*) light anaerobic infection in twenty instances and (*c*) heavy anaerobic infection in four instances. It is not clear whether Tulloch uses the term "infection" advisedly in referring to his results, for it is obvious that anaerobes may be present in a wound without evoking an infection.

COMMENT

The fact that Clostridium welchii is found so frequently in an environment with which one is in daily contact may seem to detract from the significance of its occurrence in chronic ulcerating lesions. The evaluation of the result of this study is made difficult because of an insufficient knowledge of the various factors that are necessary for the production of a clinical picture of gas gangrene. Some of the factors, other than the presence of the organism, probably involve bacterial symbiosis, local tissue phenomena, which include circulatory status, and biologic and chemical defense mechanisms. The virulence of the bacterial strain, its toxin-producing ability and the degree of anaerobiosis in which the organisms are situated are also important considerations. No attempt will be made here to evaluate these diverse influences that determine pathogenicity. That these factors are necessary is suggested by the opinion of Welch,[22] who made the first detailed description of the organism which he called Bacillus aerogenes-capsulatus. He said, "there is good reason to believe that intact tissues of human beings in health possess marked resistance to the gas bacillus." Emery [23] commented on the paradox that in a clinical case of gas gangrene, the organism is apparently very virulent, while "under ordinary circumstances the organism is almost non-pathogenic." Taylor,[24] who had a large experience with gas gangrene during the World War, and who has contributed much to the knowledge of the subject, expressed his belief that "the organism is essentially a saphrophyte."

The literature on this subject does not contain many references to civil experiences with postoperative gas bacillus infections. In 1927, Tanner [25] first pointed out the potential danger of gas gangrene com-

22. Welch, W. W.: Morbid Conditions Caused by B. Aerogenes Capsulatus, Bull. Johns Hopkins Hosp. **11**:185 (Sept.) 1900.

23. Emery, W. d'Este: Some Factors in the Pathology of Gas Gangrene, Lancet **2**:948 (May 7) 1916.

24. Taylor, Kenneth: Factors Responsible for Gaseous Gangrene, Lancet **1**: 123 (Jan. 15) 1916; Observations on the Pathology and Bacteriology of Gas Gangrene, J. Path. & Bact. **20**:384 (April) 1916; Gas Gangrene, Its Course and Treatment, Bull. Johns Hopkins Hosp. **26**:297 (Oct.) 1916.

25. Tanner, E. K.: Gas Bacillus Infections Complicating Senile and Diabetic Gangrene, S. Clin. North America **7**:1099 (Aug.) 1927.

plicating preexisting gangrene, and reported seven cases. Five of his cases showed no clinical evidence of gas bacillus infection prior to amputation. Linton (1930) emphasized the importance of this complication in the presence of any type of gangrene, and reported six additional cases. In only two cases of the six was gas bacillus infection detected prior to operation. Blake and Lahey [26] reported a case of infection with B. aerogenes-capsulatus (Clostridium welchii) which developed following amputation for diabetic gangrene. My experience with gas bacillus infections includes three cases complicating preexisting gangrene and information on two cases that developed elsewhere. There have undoubtedly been many unreported cases.

The route of infection in the cases presented and in those reported by Tanner and by Linton is not clear. Tanner attempted to isolate the organisms from the vessels of an amputated extremity and failed, but he said, "We feel sure they must have spread up the leg by way of the vessels or lymphatics to the site of amputation." Linton suggested as a possible mode of spread the thrombosed veins or lymphatics, "the organisms being in a quiescent state and stimulated to activity by trauma or other circumstances attending the amputation." Whether or not the organisms or spores may be in the tissues in a dormant state is a controversial point. Orr and Rows [27] found that bacteria left in contact with a nerve trunk ascended by the neural lymphatics as far as the cord, and could be found spreading along the posterior nerve roots. Teale and Embleton [28] found that spores inoculated into an animal may develop into vegetative forms and remain unphagocyted for a long time. In spite of reports of bacteria being found in normal tissues (Ellis and Dragstedt,[29] Reith,[30] Andrews and others [31]), the prevailing opinion is that this occurrence is not frequent. If the opinion that bacteria may be present in normal tissues is not accepted, the possibility exists of organisms being present in thrombosed veins and lymphatics or in

26. Blake, J. B., and Lahey, Frank: Infections Due to the Bacillus Aerogenes Capsulatus, With a Report of Ten Cases, J. A. M. A. **54**:1671 (May 21) 1910.

27. Orr, David; and Rows, R. G.: Toxic Infection of the Central Nervous System; A Clinical and Experimental Investigation, Edinburgh M. J. **17**:78 (Aug.) 1916.

28. Teale, F. N., and Embleton, Dennis: The Paths of Spread of Bacterial Toxins, with Specific Reference to Tetanus Toxin, J. Path. & Bact. **23**:50 (Oct.) 1919.

29. Ellis, James C., and Dragstedt, Lester K.: Liver Autolysis in Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

30. Reith, Allen T.: Bacteria in the Muscular Tissues and Blood of Apparently Normal Animals, J. Bact. **12**:367, 1926.

31. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of B. Welchii Infection in Dogs, with Sterile Bile Liver Extract and Bile Salts, Proc. Soc. Exper. Biol. & Med. **28**:136 (Nov.) 1930.

cicatricial tissue resulting from inflammation. Phocas,[32] Bazy and others made note of the occurrence of infections following surgical procedures, in which they attributed the infection to an activation of organisms latent in the tissues. Lecene and Frouin,[33] in a study of "latent microbes in the scar tissue of war wounds," found organisms in twenty-one of twenty-four wounds examined. All of these wounds contained foreign bodies, which introduces another factor; however, in four instances the foreign bodies were sterile while the surrounding fibrous capsule yielded cultures of divers organisms. These observations and the proposed route of infection as suggested by Tanner and Linton must have further confirmation, but it is probable that some such mode of infection was responsible for the cases reported here.

If this was not the method by which the gas bacillus entered the amputation stump, it must be assumed either that there was contamination from the skin of the patient or contamination from the catgut employed, or that the organisms reached the amputation stump from the intestinal tract. It is felt that the method of skin preparation was adequate to eliminate skin contamination. The catgut was of the same lot used in other operative procedures during the same period, none of which resulted in a gas bacillus infection. The intestinal route was suggested by Blake and Lahey as being responsible for their case following amputation for diabetic gangrene. The route is also suggested in a gas bacillus infection complicating a case of agranulocytosis, recently reported by Warr.[34] Weinberg, who has written a monograph on gas gangrene, expressed the belief that this route is a probable one, but this is at present a hypothesis.

Significance of Results.—One would be considered an alarmist to suggest that all chronic ulcerating lesions are potential cases of gas gangrene, for clinical experience does not warrant any such assumption. In none of the cases from which anaerobes were obtained did clinical evidence of gas gangrene develop. Most of the varicose ulcers were on extremities into which various solutions were being injected for the obliteration of varicose veins, but there is no recorded evidence that gas gangrene ever followed such a procedure. Two of the varicose ulcers (cases 7 and 23) that yielded virulent organisms were being treated by the application of sponges and tight elastic bandages. This procedure should produce approximate local anaerobic conditions and

32. Phocas: Le reveil de l'infection des plaies par l'acte chirurgical, Bull. et mém. Soc. de chir. de Paris **51**:1933 (Oct.) 1915.

33. Lecene, P., and Frouin, A.: Nouvelles recherches demontrant la réalite du microbisme latent dans les plaies de guerre cicatrisées, Compt. rend. Acad. d. sc. **162**:722 (May) 1916.

34. Warr, Otis S.: Agranulocytosis: Case with Terminal Gas Bacillus Infection, J. A. M. A. **96**:507 (Feb. 14) 1931.

favor the persistence of the bacilli. As far as can be determined, no gas bacillus infections have resulted from this type of treatment.

However, we know that gas gangrene does follow operative intervention directed to the removal of chronic ulcers; that 34.37 per cent of chronic ulcers harbor the Welch bacillus, and the relationship between their presence and the surgical procedure is suggested. Tulloch's attitude as to the significance of the presence of the anaerobes in wounds may be adopted. He said:

> One cannot assume that the presence of anaerobes, even in the later phases of the process of repair, are of no significance; for the presence of the bacilli of the Welchii group, Vibrion Septique, of B. Edematiens, and of B. tetani must always be a menace.

Gas gangrene as presented to the surgeon is usually a virulent, rapidly spreading type of infection accompanied by high mortality rate, approximately 40 per cent. In the two cases presented, although the gas bacillus infection was not the direct cause of death, it obviously was an important contributory factor. In the light of this experience, it is believed that whenever amputation is contemplated in a case in which an ulcerating lesion exists, the lesion should be cultured for anaerobes, and, if present, that polyanaerobic or specific antitoxin be given before operation. This opinion has previously been briefly expressed.[35]

Status of Anaerobic Antitoxins.—Because of the apparent hesitancy on the part of the medical profession to accept the value of anaerobic antitoxins in prophylaxis and treatment, digression will be made here to refer briefly to its present status. From 1910, when Rosenthal first attempted to prepare a serum against B. welchii, until 1916-1917, there was practically no activity in this field. The increased incidence of gas gangrene, as a result of the World War, stimulated further investigations, and the names of Weinberg and Sequin,[36] Bull,[37] Sacquepee, Leclainche, Henry,[38] Bullock and others are written into the chapter on the early development of the anaerobic antitoxin.

Some of the most convincing evidence that the antitoxins are of value is found in their use experimentally in animals. It is possible, by

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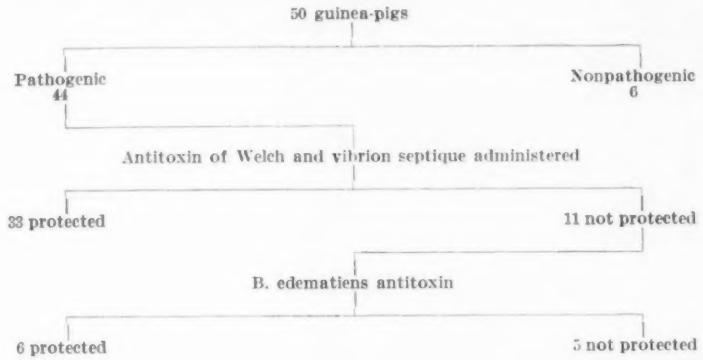
35. Manson, M. H.: Treatment of Tetanus and Gas Gangrene, Minnesota Med. **14**:142 (Feb.) 1931.

36. Weinberg, M., and Sequin, P.: La gangréne gazeuse, Monographies de l'Institute Pasteur, Paris, 1918.

37. Bull, C. G.: Antitoxin for Gas Gangrene, New York State J. Med. **106**: 821 (Nov.) 1917; B. Welchii Infections and Intoxication, J. A. M. A. **68**:1815 (June 16) 1917. Bull, C. G., and Pritchett, Ida: Toxin and Antitoxin of and Protective Inoculation Against B. Welchii, J. Exper. Med. **26**:119 (July) 1917; Antitoxin for B. Welchii, ibid. **26**:603 (Oct.) 1917.

38. Henry, Herbert: On the Antitoxin Content of Some Gas Gangrene Sera Used in the Later Stages of the War, J. Path. & Bact. **23**:270 (June) 1920.

using appropriate mixtures of antitoxin, to construct in a guinea-pig a sort of filtering mechanism, which will inhibit the development of certain organisms in the animal, and which will, at the same time, allow the growth of a pathogenic anaerobe against which no specific protection has been induced. Henry and Lacey [39] inoculated fifty guinea-pigs with cultures obtained from cases of gas gangrene. The following diagram shows the procedure and results:



Of the five nonprotected pigs, the cultures showed three infected with Clostridium fallax and two unidentifiable organisms.

Clinical evidence resulting from war experiences is offered by Sacquepee, who gave antitoxin to 319 wounded men, with a resulting incidence of gas gangrene of 1.17 per cent. In a controlled series, he reported the incidence as 7.2 per cent. In a series of 191 developed cases, the mortality in the patients treated with polyanaerobic antitoxin was 13.9 per cent, while in the same region the untreated patients showed a mortality of 75 per cent. Ivens [40] gave a polyanaerobic antitoxin to 433 wounded men among whom there were 30 cases of gas gangrene when first seen. In this series there was one death.

Opportunity for clinical verification of the efficacy of antitoxin is not frequent in civil practice and it will take time for statistics of this nature to become available. Morris, Gage, Baldwin and Gilmour,[41] Larson and Pulford [42] and other American authors all have written

39. Henry, H., and Lacey, Margaret: On the Anaerobes Responsible for Gas Gangrene in Man, J. Path. & Bact. **23**:281 (June) 1920.

40. Ivens, F.: Preventive and Durative Treatment of Gas Gangrene by Mixed Serum, Brit. M. J. **2**:425 (Oct. 19) 1918.

41. Baldwin, J. H., and Gilmour, W. R.: A Study of Gas Gangrene in Civil Surgery, Ann. Surg. **85**:161 (Feb.) 1927.

42. Larson, E. E., and Pulford, E. S.: Gas Gangrene of the Extremities with Especial Reference to Trivalent Anaerobic Serotherapy, J. A. M. A. **94**:612 (March 1) 1930.

on the subject since the war and urged that antitoxin be used. Kling [43] showed experimentally that antitoxin that is available on the market at the present time is efficient in neutralizing the antitoxins. The proposal of Williams,[44] in 1926, that the toxic symptoms of intestinal obstruction are caused by B. welchii toxins, has led to the use, in some places, of Bacillus perfringens antitoxin for this condition. It has been shown that it is of no value in intestinal obstruction, most recently and convincingly by Thurston [45] (1931), but this should in no way detract from its use in gas gangrene.

In an article on gas gangrene, Goodman [46] said:

> Death from tetanus would seem unpardonable on account of neglect of a prophylactic dose of serum administered in a case of street injury. Nevertheless, it appears that one of the most potent therapeutic measures discovered as a result of the recent world war is either forgotten or we have not had an epidemic of this gas infection brought home to us, to the realization that prophylactic measures might be applied to prevent the occurrence of such disaster.

Larson and Pulford (1930) reported seven cases of gas gangrene in which the anaerobes were controlled in every instance. Only one amputation was done; this patient died of hemolytic streptococci septicemia. In every case trivalent anaerobic serum was given, and the authors believe that serotherapy contributed largely to the success in their cases.

Experience at the University Hospital with anaerobic antitoxins in gas bacillus infections has been very encouraging. It undoubtedly aided or made possible the recovery in two cases, in one of which cultures of Clostridium welchii were obtained from the muscle on the proximal side of the amputated extremity, and also from the blood stream at the time of operation. In the other, a postoperative case of disarticulation of the hip joint, in which surgical treatment of the infection consisted only of reopening the wound and the intravenous administration of Bacillus perfringens antitoxin, a rapid recovery ensued. It is to be emphasized that antitoxin should be used to supplement, rather than to supplant, surgical treatment in a clinical case of gas bacillus infection.

The surgical treatment for gas gangrene is fairly well established, but for the sake of completeness, a summary of the essentials will be

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43. Kling, David: Treatment of Gas Gangrene with Normal Horse Serum, Ann. Surg. **91**:261 (Feb.) 1930.

44. Williams, B. W.: The Importance of Toxemia Due to Anaerobic Organisms in Intestinal Obstruction and Peritonitis, Brit. J. Surg. **14**:295, 1926.

45. Thurston, Herbert F.: The Rôle of Toxins of B. Welchii in the Toxemia of Acute Intestinal Obstruction, Arch. Surg. **22**:72 (Jan.) 1931.

46. Goodman, Charles: Gas Gangrene, Ann. Surg. **79**:806 (June) 1924.

made. In cases of massive infection, with involvement of an entire extremity, amputation is the accepted method of treatment. A tourniquet should not be used, no attempt should be made to form flaps and the stump must be left open. Meticulous care should be used to minimize trauma to muscle tissue while securing blood vessels. There is no necessity for retraction with sharp hooks or retractors. The exposed surface may be lightly covered with gauze saturated with some oxidizing agent such as surgical solution of chlorinated soda or dichloramine T. Secondary plastic operations may be necessary to make a satisfactory stump.

In localized infections, where the longitudinal spread of the process is confined to single muscle groups, excision of the involved muscle may suffice. Excellent results have been reported in this type of case by Frankau, Drummonds and Neligan,[47] Ivens,[48] Kellogg Speed[49] and Larson and Pulford.[42]

Good surgical judgment in the selection of cases is necessary. The criteria for resection are the color, contractibility and bleeding of the muscles.

Blood transfusion may be a life saving measure following amputation or débridement for gas gangrene.

SUMMARY

Two cases are presented in which gas gangrene followed amputation of extremities that were the site of chronic ulcers. Their similarity led to the question of the relationship of chronic ulcers and gas gangrene and the frequency with which ulcers harbor pathogenic anaerobes. Cultures of thirty-two ulcerating lesions revealed that eleven, or 34.37 per cent, harbored pathogenic gas-producing anaerobes. Fifty-two control cultures of normal skin yielded four cultures (7.6 per cent) of Clostridium welchii.

Clostridium welchii is the most frequent pathogenic anaerobe found in chronic ulcers. Gas gangrene complicating preexisting gangrene has previously been emphasized, and it is suggested that vigilance be extended to include chronic ulcers as a possible source of gas gangrene following surgical intervention. The possible routes of infection have

47. Frankau, C. H. S.; Drummonds, H., and Neligan, G. E.: Successful Conservative Treatment of Early Gas Gangrene in Limbs by Resection of Infected Muscles, Brit. J. Surg. **1**:729, 1917.

48. Ivens, F.: Clinical Study of Anaerobic Wound Infection and Analysis of 107 Cases of Gas Gangrene, M. Press **103**:12, 1917.

49. Speed, Kellogg: Localized Gas Infection Treated in War Wounds by Muscle Group Excision, J. A. M. A. **70**:225 (Jan. 26) 1918.

been discussed and it is believed that the most likely explanation is that the organisms were in the tissues prior to amputation. This opinion is speculative and requires definite evidence to corroborate it. Poly-anaerobic and Bacillus perfringens antitoxin has definite merit and should be more widely used. It is suggested that chronic ulcerating lesions be cultured by the use of milk as a medium, if surgical intervention is to be directed to their removal. If the characteristic stormy fermentation produced by Clostridium welchii is obtained, anaerobic antitoxin should first be administered.

ACUTE AND SUBACUTE ATROPHY OF THE LIVER AND THE EVOLUTION OF TOXIC CIRRHOSIS

A REVIEW OF TWENTY-TWO CASES *

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This paper is based on a clinical and pathologic study of twenty-two cases of atrophy of the liver. The cases have been selected as characteristic of the type of atrophy commonly designated as yellow or red atrophy of the liver (Rokitansky), and are illustrative, both clinically and pathologically, of the various stages of this type of hepatic disease.

GENERAL COMMENT

Classification.—Based on anatomic considerations, the three stages or degrees of atrophy of the liver [1] are: acute, subacute and chronic. The microscopic anatomy seen in the acute stage was characterized by extensive necrobiosis of the hepatic cells. The subacute stage followed when clearing of the cellular detritus of the acute cytolytic process appeared completed; this left a disorganized liver in which there was only partial preservation of the parenchyma. Owing to the extensive loss of hepatic cells, the hepatic stroma was brought into prominence. The chronic stage was characterized by progressive shrinkage of the dismantled hepatic stroma and likewise by regenerative rather than retrogressive changes of the parenchyma. In the latter part of the chronic stage, well defined, coarsely nodular cirrhosis was revealed. This is the end-stage or the stage of healing of acute atrophy of the liver, to which Mallory's [2] designation "toxic cirrhosis" may be applied. A consideration of the relation of this form of cirrhosis to others is not within the scope of this paper.

In an attempt to correlate this pathologic classification with the clinical features of the disease, only partial success was met with. The

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1. Marchand, F.: Ueber Ausgang der acuten Leberatrophie im multiple knotige Hyperplasia, Beitr. z. path. Anat. u. z. allg. Path. **17**:206, 1895.

2. Mallory, F. B.: Cirrhosis of the Liver; Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**:69 (March) 1911.

apparent duration of the disease, as judged by the duration of jaundice or other significant symptoms, was at considerable variance in some instances with the anatomic changes in the liver. In one case of our series, in which jaundice was of sixteen days' duration, the lesion was anatomically acute, whereas in another case, with three days of jaundice, the lesion was, by the same criteria, of a late, subacute type. Likewise, in the chronic stage, it was sometimes entirely impossible to reconcile the clinical duration with the anatomic features, as, for example, in two cases in which the lesions appeared older than the history of symptoms indicated them to be.

Inability to correlate the symptomatic age of the lesion with the anatomic age emphasizes that even in this form of hepatic atrophy considerable destructive change may occur in the liver before clinical evidence of hepatic disease appears. The degenerative process in the liver may progress to the stage just less than the maximal subclinical level, and then with a minimal added insult the hepatic disease may become manifest. If the disease is of sufficient severity, the clinical picture of icterus gravis will be evoked, but the anatomic changes characteristic of rapid hepatic atrophy may not be found. Similarly, in other cases, the disease may progress with equal slowness before it is clinically evident, as well as in the clinical phase, and reveal at the end lesions much older than seem possible when the duration of symptoms is considered. Life may endure in the acute phase, as was illustrated in one of our cases, for a considerable period (sixteen days), with coexisting extensive necrosis of the hepatic parenchyma.

Although it is impossible accurately to foretell the exact state of the liver, as judged by the duration and severity of the symptoms, nevertheless a clinical classification should exist. The only approach to this must be on the basis of duration and severity of symptoms; although they may not always be in accord with the anatomic features, they may give a relatively useful indication to the clinician of the stage of the disease. Since jaundice is the most constant symptom that these patients present, it is perhaps the best clinical guide. Ascites is relatively latent and always denotes, according to the anatomic classification we have used, a chronic stage.

We observed only one case of acute atrophy, and in this the duration of symptoms was sixteen days. Nine cases of the subacute stage, with the clinical duration of from three to thirty-four days, were reviewed. Twelve cases were of the chronic group. In these cases the clinical duration was from thirty-two days to three years. The average life expectancy for the entire series of cases, as based on the duration of jaundice, was fifteen weeks. Fifteen of the twenty-two patients, however, died two months after jaundice first appeared.

ETIOLOGIC CONSIDERATIONS

Although many different etiologic agents have been found associated with acute atrophy of the liver and with the related subacute and chronic types, the pathologic anatomy in cases of differing causation is similar. Variations in the anatomic picture are chiefly quantitative. Most cases of hepatic atrophy, in spite of the large number of substances reported as etiologic factors, develop without adequate etiologic explanation. Whether all cases will eventually be shown to be due to an exogenous toxic substance is doubtful. Endogenous or metabolic toxins may eventually prove to be of decided importance.

It is apparent from a careful analysis of cases, especially those due to a known agent, that in addition to the toxic factor, some fundamental unknown constitutional state, perhaps transient and of metabolic character, also enters into the etiology and pathogenesis. This fact is shown by the varying degrees of susceptibility patients exhibit to toxic substances which are known sometimes to induce hepatic atrophy. In experimentally produced hepatic necrosis, Opie and Alford,[3] Graham,[4] Davis and Whipple[5] and Simonds[6] have shown that the available dextrose and the hepatic glycogen afford considerable protection to the liver against injury, and, further, that regeneration progresses more favorably when carbohydrate is abundantly supplied in the diet. This may explain in part the varying degrees of susceptibility that patients exhibit.

Of the substances reported to produce these hepatic changes in man or animals may be mentioned cinchophen, chloroform, mercury, arsphenamine, arsenic, phosphorus, trinitrotoluene, trinitrophenol, tetrachlorethane, dinitrobenzene, Aspidium, lupine toxins, Amanita phalloides toxin, carbon tetrachloride, chiniofon (N. N. R), toxic hyperthyroid states, toxic products of pregnancy, bacterial toxins, alcohol in large quantities, hemagglutinative serums and cystine.

A toxic substance as an etiologic factor could be found in seven of our cases. In five cases it was cinchophen, and in two cases arsphenamine. In the remaining fifteen cases a definite etiology could not be established. Of possible significance, in relation to antirheumatic drugs,

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3. Opie, E. L., and Alford, L. B.: The Influence of Diet on the Hepatic Necrosis and Toxicity of Chloroform, J. A. M. A. **62**:895 (March 21) 1914.

4. Graham, E. A.: The Resistance of Pups to Late Chloroform Poisoning in Its Relation to Liver Glycogen, J. Exper. Med. **21**:185 (Feb. 1) 1915.

5. Davis, N. C., and Whipple, G. H.: The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, Arch. Int. Med. **23**: 612 (May) 1919.

6. Simonds, J. P.: The Mechanism of the Protective Action of Carbohydrate Diets in Phosphorus and Chloroform Poisoning, Arch. Int. Med. **23**:362 (March) 1919.

is the fact that besides the five cases in which there was a history of some type of rheumatic, arthritic or neuritic pain, and in which there was a history of the patient having taken cinchophen for its relief, there were seven additional cases in which there was a similar history of pain, but in which there was no admission by the patient that drugs had been taken. The inference that might be drawn from this is that cinchophen, or proprietary preparations containing it, might have been used, but information of its use was not obtained from the patient. In only one of these seven cases was any type of treatment for the rheumatic pain admitted, and this was some form of intravenous injection of autogenous blood after it had been allowed to stand. The possibility that this might have been significant is shown by experiments of Pearce,[7] and others, although somewhat different, who produced severe hepatic necrosis in animals by the injection of hemagglutinative serums.

In three cases the condition so closely followed acute respiratory infection that the possibility of the infection playing some part must be considered. In one case [7a] the patient had given a severe reaction to influenza vaccine three years before jaundice developed. In one case the hepatic condition followed shortly after operative intervention for ventral hernia, at which time a gallstone was removed from the gallbladder, and it was noted that the liver was normal. If the hepatic changes followed the operation, the possibility of the anesthesia inducing the changes must be considered.

In four cases a clue to etiology could not be found, with the possible exception that in one case there was an ancient history of syphilis, but without clinical or pathologic evidence of its presence or any history of treatment, and that another case followed a severe emotional upset. The older writers believed the latter to be significant in the etiology.

The relation of concurrent disease involving the upper part of the intestinal tract is fairly striking. Seven patients complained of epigastric distress for a considerable time preceding the actual development of symptoms of hepatic atrophy. Three of these patients had duodenal ulcers; in one they were associated with cholelithiasis, and two other patients had cholelithiasis only. Two patients did not present

7. Pearce, R. M.: The Experimental Production of Liver Necroses by the Intravenous Injection of Hemagglutinins, J. M. Research **12**:329, 1904.

7a. In several places in this paper, the analytical reader will experience difficulty in adding the number of cases mentioned in different categories to a total that is consistent with that given for the group which includes those categories. The reason for this difficulty is that some cases necessarily have been mentioned twice. For instance, a patient who had arthritis also had infection and it was necessary to mention her once in connection with each condition. This apparent discrepancy seemed less objectionable than the circumlocution that would have been necessary to avoid it.

anatomic evidence that would account for the epigastric distress. Cholelithiasis or cholecystitis was also found in three other cases, but without history of previous epigastric trouble.

In one case, besides cinchophen, toxemia of pregnancy may have played a part, but this is the only case in which there was a probable relation to pregnancy.

In none of the cases was there alcoholic addiction, and in only five cases was the use of alcohol admitted.

In two cases only was there laboratory, clinical or pathologic evidence of syphilis.

Youth or an early adult age, as other investigators have found, was not a predisposing factor in this series of twenty-two cases, for the ages of the patients varied from 7 to 66 years, the average age being 48 years. Only two patients in the group were less than 30 years old.

The sex incidence shown in previously reported cases is maintained in this series, in which fourteen cases affected females and eight affected males.

CLINICAL ASPECTS

The symptoms were characterized by either a rapidly fulminating course advancing to death or a slowly progressive course. It is rather difficult for that reason to describe the cases as a whole. This is possible, however, if it is appreciated that the course of the disease may be completed in a few days, or that it may progress in a mild form with similar symptoms until severe hepatic insufficiency ensues. As a terminal manifestation the symptoms of acute, fulminating atrophy usually present themselves.

Initial Symptoms.—At the beginning of the illness, jaundice was present in twelve cases. In four cases it was the only initial complaint. As an accompaniment of icterus, pruritus was complained of by six patients, and seven had noted acholic stools and dark-colored urine. Malaise, suggested by lassitude, mental depression, headache, weakness or anorexia, usually an accompaniment of the jaundice, appeared in fifteen cases as a first symptom; malaise appeared as the principal initiating symptom without jaundice four times.

In eleven cases there were abdominal distress, usually a vague, mild abdominal pain, fulness in the epigastrium, flatulence, nausea or vomiting. In only three cases, however, was vomiting elicited in the history, and never hematemesis. In four cases pain over the region of the liver was definitely mentioned. As the only prodromal complaint, abdominal distress was recorded in three cases. In one case, chills and fever, with malaise and abdominal distress, were recorded as being the beginning of the illness. In only one case was the condition fulminating at the onset, progressing rapidly to death in four days.

Progressive Symptoms.—Although jaundice was found in only twelve cases as an initial symptom, its development in our cases became universal with progression. In the cases in which it was delayed, judged by the apparent clinical beginning of the trouble, it became evident in from one to thirty-five days after the onset of illness; the average period before its appearance was thirteen days. In five cases there was history of some fluctuation of the icterus, usually with one period of remission, but in none did the pigment completely leave the skin or sclera. In one of the cases all characteristics of the illness were subject to exacerbation and remission, and jaundice followed the same tendency. In all but these five cases, the degree of jaundice was progressive up to a maximal level, with some fluctuation of the curves of serum bilirubin at the higher levels, but without much corresponding change in cutaneous pigmentation. In all but five cases light-colored to clay-colored stools were observed, but frequently only in the terminal stages of the illness did the clay color of the stool correspond in degree to the relatively high values for serum bilirubin. Duodenal drainage and tests for bile in the stool usually gave evidence of the presence of bile, but in two instances duodenal drainage was negative for bile late in the course of the disease when earlier it had been positive. Pruritus as an accompaniment of icterus was found in only nine cases. A purpuric tendency was observed in five cases, although hemorrhages were almost always found at necropsy.

Since most of the patients came to the clinic late in the course of the disease, there was usually no difficulty in predicting the termination of the illness. In two cases, however, because of the apparently mild systemic reaction accompanying the icterus, the probability of the disease terminating fatally was not entertained. That in these cases the disease was of the simple catarrhal type was given further credence when the jaundice began to clear up. As events subsequently revealed, one patient was susceptible to cinchophen, and the remission experienced was probably due to discontinuance of the drug. On the patient's returning home, however, resumption of use of the drug caused exacerbation of hepatic changes, which progressed to a fatal termination. In one case there was no history of the patient's having taken drugs, and the icterus in the beginning was clearly not of the grave type. In one case it was fairly well established on the patient's first admission that the jaundice was the result of the toxic effect of oxyliodide, and although a guarded prognosis was given, this patient might have recovered had advice to discontinue the use of the drug been adhered to.

Since in many of our cases, illness developed and the patient died before the van den Bergh reaction was generally applied, readings of this reaction were obtained in only thirteen cases. In all of these the

reaction was direct. Values for serum bilirubin were obtained in the same number of cases. The degree of icterus, as judged by this quantitative procedure, usually appeared to be a criterion of prognosis and an indication of the condition that would be found in the liver at necropsy. In four cases jaundice seemed especially to correspond in its degree to the progress of the disease. The highest degrees of icterus were present, as a rule, in the cases in which the course was more rapid, especially in those terminating in the acute or early subacute stages, in which values for serum bilirubin up to 39 mg. for each 100 cc. of blood were sometimes shown. In some cases there was a fall from a previous high level as the patient entered the terminal stages of the disease.

Studies of blood coagulation time gave conflicting results in this series of cases. In some instances, its increase was substantially apparent with an unfavorable turn in the condition of the patient, but as a rule its tendency to increase was by no means as marked as in extrahepatic obstructive types of jaundice, and could not be relied on as a ground for predicting that hemorrhages would be found at necropsy.

In one case only was there a history of jaundice previous to that associated with the last illness.

As in the prodromal stages of the disease, and also in its progress, abdominal distress was often an annoying complaint. Anorexia, heavy feeling in the epigastrium, epigastric soreness, dull pain or light stitches of pain along the right costal margin, intolerance to food or nausea at some time, although this fluctuated to some degree, were present in all cases. In only fourteen of the cases did vomiting enter into this picture, and in only one case was there blood in the material vomited.

Although pain approaching the nature of colic, typical of intraductal occlusion by a calculus, was never observed with the appearance of jaundice, it did appear in the progress of the disease in seven cases. In four cases, it resembled closely the pain of colic from biliary calculus. In one of these, besides pain there were fever, leukocytosis and abdominal rigidity, which further added to the complications of diagnosis. In two cases there was accentuation of the jaundice with the attacks of colic, and in two cases morphine was required for relief of pain. In these respects there was similarity to the pain occurring in obstruction of the biliary ducts from calculus. Usually there was only one attack of pain, which disappeared without marked improvement in the jaundice and without leaving marked residual soreness. The opposite would have been expected had the pain been of the type produced by obstruction from a calculus. The rare association of chill and fever in cases of atrophy is a further differential sign. In one case only were calculi

found at necropsy as a basis for the pain, and in that case, although the gallbladder was filled with stones, evidence was not at hand to indicate that any of them had been passing through the ducts. It must be concluded from a review of our cases that pain as a feature of intrahepatic jaundice at times forms a rather conflicting picture, and serves to confuse the diagnostician who might suspect that the jaundice is due to obstruction of extrahepatic bile ducts by calculi.

In all cases dealt with in this group, weakness, progressing eventually to a state of exhaustion, constituted a significant part of the clinical state. In the subacute and chronic types of the disease this progression was slow and was subject to exacerbations and remissions that correspond with the general fluctuations of the disease. The extreme weakness was always the signal of impending hepatic insufficiency and the approach of a fatal state.

Loss of weight usually was noted by the patients, and was often related to loss of appetite. Hepatic atrophy apparently has no predilection for either the obese or the thin person, for extremes in weight in both directions were noted throughout the series of cases.

For the most part, these cases ran an afebrile course, or at least the temperatures were below 100 F., usually with some depressions below normal. In one case there were initial chill and fever for one day, and in another, with the reappearance of jaundice after remission, a temperature of 103 F. was experienced. During their stay in the hospital three patients had fever, but only in one case was this troublesome.

The pulse was little changed until signs of fatal hepatic injury became manifest as a part of the toxemia; then it became rapid and weak. Early in the disease slight slowing sometimes was observed.

Ten cases were observed in which there was tenderness over the liver or in the epigastrium. The liver was definitely small in eight cases. In three cases the reduction in size of the liver during observation was a noteworthy diagnostic and prognostic sign. In one of these, with the initial appearance of jaundice, the liver was thought to be reduced in size; several months later, after a remission and in a period of exacerbation, it appeared enlarged. But a few days later, it was again found to be reduced in size. Additional evidence was furnished in two cases that the liver may be larger than normal until a short time before the end. Too much emphasis as to diagnosis cannot be placed on the size of the liver, for in obstructive jaundice it will be found large at first and later smaller, although the reduction in size occurs perhaps with less rapidity than in atrophy.

Ascites was present in almost all of the cases of the chronic type. In one case (the earliest in which it appeared clinically), it was noted on the twenty-fifth day after the onset of symptoms; death occurred on

the thirty-second day of the illness. Ascites was observed in eight additional cases. Its absence in the case of three years' duration was the greatest contradiction to its constancy in delayed cases.

Neither severe constipation nor serious diarrhea was observed with any frequency. Perhaps the greater tendency was to constipation, but in one case severe diarrhea was complained of.

Estimations of the concentration of urea in the blood did not as a rule offer much help in estimating the severity of hepatic degeneration. In one case in which death occurred within four days after the onset, the value for blood urea was 24 mg. in each 100 cc. Exceedingly low figures were obtained in only two cases in which, on two analyses, values of only 9 and 10 mg. in each 100 cc., respectively, were found.

Values for blood sugar were below ordinary normal levels in only three cases, in which they receded to 50, 54 and 76 mg. in each 100 cc. The administration of dextrose in the treatment may have been to some degree responsible for maintenance of normal values in the other cases.

Urinalysis usually revealed albumin in moderate amount, but in seven cases none was found. Casts and erythrocytes were also occasionally found. The presence of blood was usually an indication, as confirmed at necropsy, of pelvic or vesical hemorrhage. Tests for bile in the urine were obviously always positive. Microscopic search for crystals of leucine and tyrosine was made in five cases, but these substances were never found.

Moderate to moderately severe grades of secondary anemia were frequently observed, but anemia was never an alarming feature, except in one case in which hemorrhage constituted the immediate cause of death.

The Terminal Stage.—For a variable period after the development of jaundice, weakness, malaise, anorexia and abdominal distress, the condition appeared to remain constant, with perhaps some tendency to temporary remissions or exacerbations, but without actually becoming much more severe. Usually the patients had remained at home until the inception of the terminal stages. They were more or less ambulatory and under the care of their local physicians, evidently not appreciating that eventually a critical turn in their course would come.

The initial and progressive stages may be exceedingly short in the fulminating cases, as in one case in which prodromal manifestations were present for only one day, or they may slowly progress for weeks, months or years. Reparative processes were so completed in one case that the illness for which the patient entered the clinic concerned only remotely that which related to hepatic atrophy. In this case the patient was suffering from carcinoma of the stomach, and directed her complaint almost entirely to this.

The progressive cases of jaundice, in which there was no tendency to improvement, sooner or later advanced into the serious stage of severe hepatic insufficiency. When this stage was reached, the prognosis became universally grave, for recovery did not occur. This turn was usually not abrupt, but gradual. Weakness was accentuated, progressing to exhaustion, the abdominal complaints became more troublesome, jaundice almost always became intensified, and changes in the mental state appeared. When finally hepatic insufficiency had progressed to a fatal state, mental changes appeared most marked, progressing through dulness to mental confusion, stupor and delirium. Semicoma, rapidly deepening to coma, always signified the end. With these changes there were sometimes generalized muscular twitchings or actual convulsions, as shown in six cases of the series. In one case hematemesis was severe. Fever, with a temperature of from 100 to 108 F., was present in thirteen cases as a terminal manifestation; in other cases the temperature was practically normal to the end. With the rising fever or other increased toxic manifestations, the pulse rate became rapid and feeble, and acceleration to from 100 to 140 beats a minute was the rule. In spite of the earlier low and normal values for blood urea in many cases, at this time there was a rise; in this series the maximal amount was 106 Gm. in each 100 cc. With this there was diminution of urinary output, which progressed in a few cases to almost complete suppression. In one case there was profuse sweating at the end. Leukocytosis sometimes accompanied this final stage; in five cases the leukocyte count ranged from 10,200 to 24,000.

The mean duration of this stage, from the time of appearance of its subjective signs until death, as nearly as could be estimated, was twelve and a half days; the spread was from one to thirty-three days. After the development of the more profound mental changes, duration of life was a matter of only a few days.

SURGICAL ASPECTS

The combination of pain with jaundice usually denotes obstruction of the common bile duct by a calculus. That this should be a not uncommon occurrence in the subacute and chronic stages of hepatic atrophy forms the most frequent justification for exploration. Although exploration has not proved to be of any particular value in cases of unmixed hepatic atrophy, and although there is some evidence that it has been harmful, there is, nevertheless, always the possibility that the surgeon may discover a condition such as the presence of gallstones; these, if found, really are responsible for the trouble, and removal will effect relief.

Other investigators have reported experiences similar to those met with in three cases of our series, in which the diagnosis of primary

hepatic atrophy was ascertained with certainty only by laparotomy. Umber,[8] Huber and Kausch,[9] Strauss,[10] Braun,[11] Brütt,[12] Römer,[13] Pool and Bancroft[14] and Whipple[15] have reported cases of this type.

Braun stated that in his experience drainage of bile causes much improvement. In Römer's case, marked improvement was exhibited after laparotomy; apparently the patient recovered completely. Whipple would not operate if the diagnosis could be clearly established by other means, although he thought it not harmful to prove the diagnosis in this way. The latter is probably the more acceptable position.

Probably the most significant differential diagnostic point distinguishing unmixed atrophy of the liver from obstructive lesions of the biliary tract is that in hepatic atrophy bile is persistently found in the material obtained by duodenal drainage of deeply jaundiced patients who usually have associated severe toxemia. Another significant fact shown by this study is that severe pain was never an initial accompaniment of the icterus, and chills and fever were extremely rare, having been recorded in only one case in the series with the onset of jaundice.

PATHOLOGIC ANATOMY

Macroscopic Changes.—In this series of cases, atrophy of the liver was the outstanding pathologic change observed on macroscopic examination. The smallest liver found in an adult weighed 640 Gm.; jaundice had persisted for twenty-nine days. The average weight of the livers for the entire group was 955 Gm., excluding the weight of a child's liver. Although atrophy was a distinctive characteristic, the weight of the liver was rather variable throughout the study. In the acute and early subacute cases, and to some extent in the cases of longer duration, the atrophy was not extreme. It appeared to reach its maximal low

8. Umber, F.: Zur Klinik der akuten beziehungsweise subakuten Leberatrophie, Deutsche med. Wchnschr. **1**:537 (May 15) 1919.

9. Huber, O., and Kausch, W.: Zur Klinik der subakuten Leberatrophie, Berl. klin. Wchnschr. **1**:81 (Jan. 7) 1920.

10. Strauss, H.: Ueber subakute Leberatrophie mit Aszites und dessen Beziehungen zur Leberzirrhose, Deutsche med. Wchnschr. **1**:487 (April 29) 1920.

11. Braun, W.: Chirurgische Eingriffe bei akuter und subakuter Leberatrophie, Klin. Wchnschr. **1**:2510 (Dec. 16) 1922.

12. Brütt, H.: Zur Frage der Spontanheilung der subakuten Leberatrophie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **36**:29, 1923; abstr., J. A. M. A. **81**:259 (July 21) 1923.

13. Römer, C.: Beitrag zur Frage der Heilung der Leberatrophie, Virchows Arch. f. path. Anat. u. Physiol. **254**:229, 1925.

14. Pool, E. H., and Bancroft, F. W.: Atrophy of the Liver with Nodular Hyperplasia, Surg., Gynec. & Obst. **37**:44 (July) 1923.

15. Whipple, A. O.: The Clinical Course of Subacute Yellow Atrophy as Observed in Two Proven Cases, Am. J. Surg. **6**:655 (May) 1929.

level in three cases in which the atrophy was of the late subacute stage, and to be considerably increased in the early chronic stage, although in the subacute group there was considerable variation in weight from case to case. In the late chronic cases, there usually were uniformly small livers; except in two cases, the weight was well under 1,000 Gm. Atrophy frequently was more pronounced in the left lobe.

The color of the liver, even in the early cases, was variable. The pure yellow or pure red atrophy, as described by Rokitansky,[16] rarely existed. In our cases there usually was a mottled red and yellow appearance. The yellow color, as it existed in the degenerating parenchymal units, frequently shaded to green, representing the oxidation of bilirubin to biliverdin. The red regions, which usually were extensive, represented the zones of total parenchymal destruction, with the detritus of the necrotic hepatic cells cleared away. The red was due to blood still circulating through these skeletonized lobules, and the shade of red apparently depended on the thoroughness of this continued circulation, for in the late cases with the impairment of circulation the color changed to grayish red.

The consistency of the livers was variable throughout the series. It appeared to depend on the degree of parenchymal destruction and on the amount of condensation of the hepatic framework. It also was found to vary with the size and number of the regenerating nodules. In the acute and early subacute cases, the entire liver was soft, later becoming leather-like and finally very firm. The Glisson capsule became opaque and thick.

Evidence exists to show that the yellow nodules, as seen in the cases of chronic atrophy, are an expression of parenchymal regeneration following destruction. The evolution of these nodules was well shown in cases of varying duration. The younger, regenerating nodules appeared as tiny yellowish or greenish-yellow portions, becoming evident as tiny flecks, or as ill defined individual or aggregated lobules in a reddish-brown ground substance that was devoid of lobular markings, except as central veins might demarcate the lobules in a liver that was the site of chronic passive congestion (fig. 1). Beneath the capsule they gave the liver a mottled or blotchy yellow appearance, or rose from the red, capsular surface as small yellow granules. The cut surface gave the same appearance, but the nodules were frequently seen more prominently gathered about visible blood channels. They were much more prominent in the right lobe than in the left. In the subacute stages, it was impossible to distinguish between the remains of the hepatic lobules and beginning regeneration. There was considerable

16. Rokitansky, Carl: A Manual of Pathologic Anatomy, London, Sydenham Society, 1849, vol. 2, p. 122.

variation in the degree of the nodular development; the nodules of larger size appeared in the late cases of chronic atrophy (figs. 2 and 3). In their late development, nodules from 0.5 to 2 cm. in diameter were the rule, although in some cases (figs. 4 and 5) the huge nodular development simulated the gross appearance of hepar lobatum.

Histologic Changes.—The composite histologic picture in this group of cases of atrophy consisted of three outstanding changes, namely, retrogression, regeneration and changes in the hepatic stroma. The predominating change depended on the stage or age of the lesion, that is, on whether it was acute, subacute or chronic. Throughout all of the stages there was extensive atrophy of the hepatic parenchyma, at first necrosis, then recovery of small groups of hepatic cells from the toxic influence and finally parenchymal replacement through regeneration.

Fig. 1.—Early chronic atrophy of the liver. The light areas (*a*) represent the zones of complete parenchymal destruction, with contraction of the hepatic stroma ("red atrophy"). Congested skeletonized lobules are represented by the dark areas (*b*). Beginning regeneration of hepatic parenchyma is shown in the form of small nodules (*c*).

Since the prominence of the connective tissue was due to loss of hepatic cells, the framework of the liver thus being brought into view, the changes in it also followed with the age of the lesion; at first there was a network of reticulum; later this contracted to present the appearance of fibrosis. The toxic effects were apparently directed solely against the hepatic cells. The bile ducts were preserved, and the connective tissue structures withstood the insult without reacting to it. Since the connective tissue of the liver was uninjured, its part as a replacement tissue was mostly passive.

In the acute stage the parenchymal retrogressive changes dominated the picture. Various stages of cellular degeneration, to extensive necro-

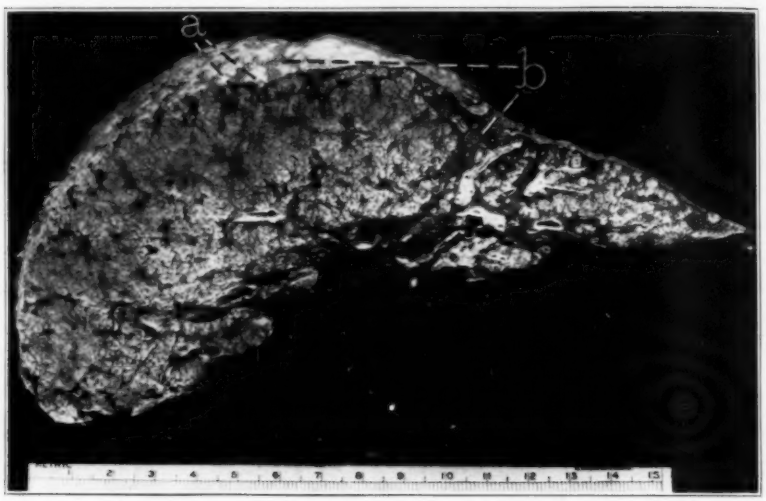

Fig. 2.—Chronic atrophy of the liver (early toxic cirrhosis); (*a*) regenerated nodules of hepatic parenchyma; (*b*) hepatic stroma somewhat contracted ("red atrophy").

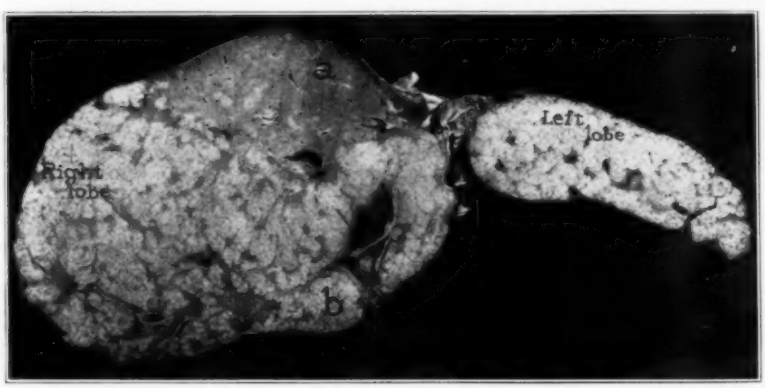

Fig. 3.—Chronic atrophy of the liver (toxic cirrhosis); (*a*) large red area devoid of parenchyma, consisting of contracted hepatic stroma; (*b*) nodules of regenerated hepatic parenchyma.

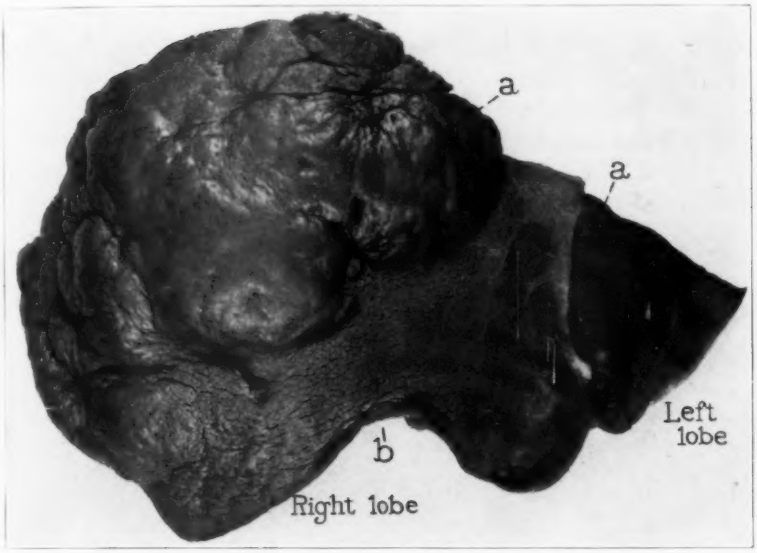

Fig. 4.—Chronic atrophy of the liver (toxic cirrhosis of large multinodular hyperplasia type); (*a*) large nodule of regenerated hepatic parenchyma; (*b*) "red atrophy"; this area is composed of shrunken hepatic stroma, in which there has been almost complete destruction of the hepatic parenchyma. Regenerative nodules are absent.

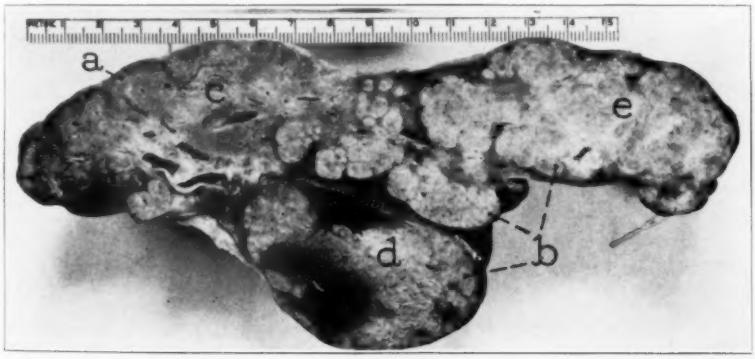

Fig. 5.—Chronic atrophy of the liver (toxic cirrhosis). Marked deformity of the organ due to irregularity of regeneration; (*a*) "red atrophy" without regeneration, consisting of contracted hepatic stroma; (*b*) regenerated nodules of parenchyma; (*c*) right lobe; (*d*) caudate lobe; (*e*) left lobe.

biosis, were seen (fig. 6). In the necrotic zones the cells stained faintly and appeared to be undergoing lysis. Polymorphonuclear and mononuclear phagocytic leukocytes pervaded the peripheral lobular zones and extended to some extent into the region occupied by the necrobiotic cells. Necrosis appeared to be more extensive in the central lobular regions than at the lobular periphery. In a few regions, either partial or complete clearing of the degenerated cells had been effected. Wherever this had occurred there remained a markedly congested sinusoidal bed, the

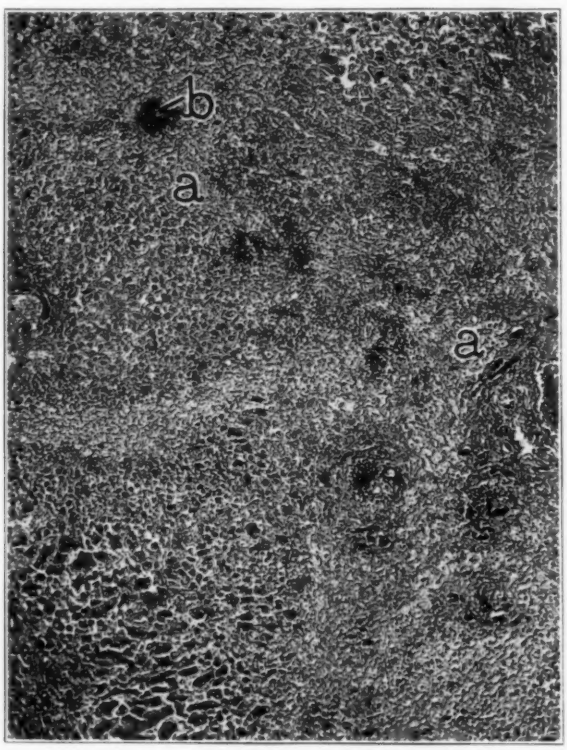

Fig. 6.—Acute atrophy of the liver, revealing extensive lobular necrosis and disorganization; (*a*) where the cellular detritus has been cleared, the sinusoids and reticulum are prominent; (*b*) or congested; prominent periportal bile ducts are seen in the middle right portion. Hematoxylin and eosin; × 65.

original reticulum of the lobule having been dismantled and appearing as a bare connective tissue framework.

In the subacute stage the markedly disorganized state of the liver, owing to the preceding necrosis of hepatic cells, was prominent (fig. 7). The picture presented by this disorganization varied in different microscopic fields in the same case and in the various cases of the group. Small clusters of hepatic cells were sometimes seen surrounding the

periportal connective tissue. In other regions, the hepatic cells appeared singly or were arranged in a partially intact hepatic cord, whereas in still other cases or other regions of the same case, nearly intact lobules could be found, but usually with dismantled portions about the central vein or with bands of lobular dismantling existing between the portal and central veins. In a few cases it appeared as though the necrosis was progressive, but usually it was either ended or so mild and slowly progressive that its presence was not distinguishable by histologic methods. The disappearance of the hepatic parenchyma left the peri-

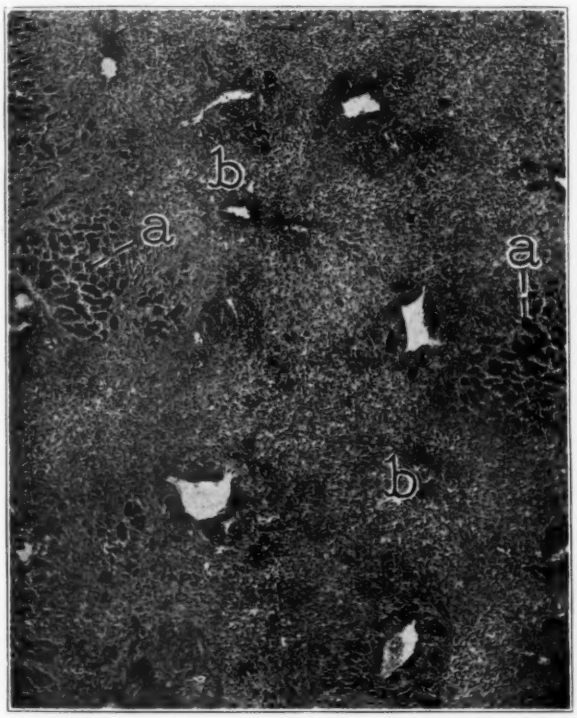

Fig. 7.—Subacute atrophy of the liver; (*a*) the isolated group of hepatic cells, nestled at one side of the intralobular zones. The detritus of the necrotic hepatic cells has been cleared at (*b*) leaving the framework of the liver very conspicuous (grossly red areas). Bile ducts are prominent in the periportal zones owing to the loss of surrounding hepatic cells. Hematoxylin and eosin; × 75.

portal biliary ductal structures dismantled, so that they were very prominent. Although in some instances the number of bile ducts appeared to be increased, it was not possible definitely to ascertain that the increase was due to actual ductal proliferation. The appearance of intralobular proliferation of bile ducts, in many instances at least,

resulted from the retrogression of hepatic cords, which seemed sometimes to assume tubelike formation.

In the older cases of subacute atrophy there was evidence of regeneration of hepatic parenchyma beginning from the better preserved groups of hepatic cells (fig. 8). Regeneration, however, was never marked at this stage. In places where lobular dismantling had occurred, the connective tissue was composed of the original hepatic stromal substances, somewhat contracted but still arranged so that lobular identi-

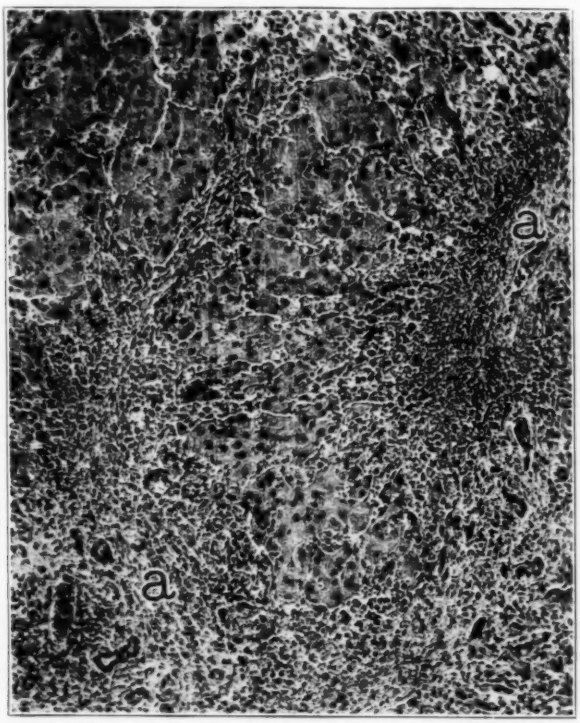

Fig. 8.—Subacute atrophy of the liver. Group of regenerating hepatic cells in an intermediate lobular position, apparently cut off on either side; (*a*) both periportal and central lobular zones are dismantled; in the dismantled areas congested sinusoids are prominent. Bile ducts are conspicuous in the periportal zone (lower left). Hematoxylin and eosin; × 100.

fication was possible. The sinusoids of such skeletonized lobules were frequently congested, but sometimes there had been sufficient stromal contraction to occlude them. Lymphocytes and other mononuclear leukocytes were collected beneath Glisson's capsule and in the periportal connective tissue; these, however, were never numerous. Interference with the flow of bile frequently resulted in the formation of bile thrombi in the biliary canaliculi of the hepatic cords or in the intralobular tube-

like structures. Lipoids were frequently observed in the hepatic cells that remained in group formation but more especially in the retrogressive isolated hepatic cells, miniature cords or intralobular tubelike structures.

In the chronic stage evidence of retrogression was rarely to be observed in the hepatic cells, but, on the contrary, regeneration prevailed (fig. 9). This was most evident in the cases of the late chronic group, but its gradual evolution, beginning in the late subacute stage and progressing throughout the chronic series, was apparent. Regeneration

Fig. 9.—Chronic atrophy of the liver (early toxic cirrhosis); (*a*) structures resembling tubules are prominently displayed about the periphery of the lobules; (*b*) nodules of regenerating hepatic cells; the hepatic stroma is shrunken, with sequential narrowing of the sinusoidal bed. Hematoxylin and eosin; × 65.

usually proceeded from the better preserved groups of hepatic cells, and appeared to occur by a process of hypertrophy and hyperplasia of the cells, although the actual evidences of cellular growth were difficult to find. The regeneration occasionally appeared to come also from the hepatic cells of the small, previously mentioned, intralobular, tubelike structures. Regeneration by this means, however, was exceptional.

The regenerating lobules formed as nodules of hepatic parenchyma. The hepatic stroma appeared to be contracted by the nodular growth. There was no evidence that it was invaded by the growth. The connective tissue became progressively shrunken, in the cases of longer duration, until a dense connective tissue was revealed, usually, though, with identification of the skeletonized lobule still possible. This contraction was accentuated where the stroma was impinged on by growing nodules of parenchyma (fig. 10). As shrinkage of the connective tissue

Fig. 10.—Chronic atrophy of the liver; late stage of toxic cirrhosis. The hepatic stroma is compressed by regenerated lobules of varying size in nodular formation. Van Gieson stain; × 35.

advanced, the formerly patulous sinusoids were closed, and periportal biliary ducts and intralobular tubelike structures appeared to atrophy with it. Lymphocytic collections in the periportal connective tissue and in the skeletonized lobules were rarely abundant. In the cases of subacute and chronic atrophy, although the clinical termination of the disease usually suggested an exacerbative hepatic change, this appearance was never confirmed in the histologic studies of the liver. Evidences of fresh extensive necrosis of cells were never found.

Ascites and Jaundice.—This description would not be complete without suggested explanations of the development of ascites and jaundice in the presence of this lesion. Anatomic evidence points to the ascites as being due to portal obstruction caused by the closing down of the sinusoidal and intralobular venous circulation. Its early appearance, before changes in the better supported portal veins had occurred, suggests that it was not necessarily dependent on narrowing of the portal veins themselves. In later stages, however, hyaline changes, with thickening of the portal veins, indicate that eventually they too entered into the process of obstruction.

The presence of bile thrombi in the bile canaliculi gave the impression of obstruction to the flow of bile. This could be accounted for on the basis of disorganization, rupture or crowding of the hepatic cords. Obstruction due to cholangeitis was never found. Much more important than obstruction, however, in the production of jaundice in these cases of hepatic atrophy was the diminution of hepatic parenchyma, which holds not only for the acute stages but for the subacute and chronic stages.

Anatomic Changes in Other Organs.—The initial toxic substances exerted but little effect on other organs than the liver. Degenerative changes occurred in them, probably because of metabolic toxins that accumulated as a result of the hepatic dysfunction.

The kidneys at the time of death were usually involved in an acute, diffuse, toxic type of degenerative change characterized by swelling and intensive bile staining. The bile pigment could be seen in the tubular epithelial cells and within tubules in the form of bile-stained casts. The epithelial cells of convoluted tubules and Henle's loops were swollen, granular and vacuolated, sometimes showing evidence of necrosis and desquamation, and usually containing fine droplets of fat. Glomeruli were apparently not involved. Sometimes, except for bile staining, the kidneys appeared to be normal. In the kidneys in one case, extreme fatty change with fat within tubular cells and the tubular lumens was observed.

The pancreas appeared to be normal in half of the cases. It showed evidences of chronic changes characterized by atrophy and interstitial pancreatitis in seven cases. In five cases there was an acute change characterized by fat necrosis and polymorphonuclear leukocytic exudation. This was never severe, but rather of focal type.

The spleen weighed 200 Gm. or more in only six cases, and in only two cases was the weight more than 300 Gm.; in one case the weight was 340 Gm., and in one it was 975 Gm.

Ascites was found in the early cases only occasionally, and was extremely mild; usually there was none. Its absence was apparently not connected with duration or the exact fibrotic state of the liver, for it was not present in two cases that were representative of the relatively late cirrhotic stages. In these cases, its absence was probably to a considerable extent dependent on development of collateral circulation, although at necropsy evidence of this was not clear.

The thyroid gland was examined in eleven cases, and in these it was normal, except for mild hyperplasia of epithelial cells in one case; in another case there was only a small fetal adenoma.

The heart muscle usually was the seat of a moderately severe fatty degenerative change. Usually small epicardial or subendocardial petechial hemorrhages were seen.

Hemorrhages, as represented by purpuric spots on the skin, or petechiae on the pleura, peri-endocardium, peritoneum, mucosa of the intestinal tract or in the mucosa of the genito-urinary tract, were almost constantly found.

In fifteen cases, passive congestion of the lungs existed, in four of which definite evidence of terminal bronchopneumonia was observed.

In the suprarenal glands there was anatomic evidence of pathologic change in only three cases. In two cases there were small zones of deposition of calcium in the medulla and in one case a small adenoma of the cortex.

None of the cases revealed the existence of old or previous hepatic disease. Previous changes could easily have been obscured by the atrophy, but old fibrosis resulting from injury should easily have been detected in the sections subjected to the van Gieson stain.

SUMMARY

Clinical and pathologic study of twenty-two cases of atrophy of the liver revealed a common pathogenesis but probable widely differing etiology. The lesion begins in relatively rapid atrophy of the liver, and, according to severity and rapidity of the atrophy and associated changes, may be revealed as an anatomically acute, subacute or chronic lesion. Progression into the chronic stage is dependent not only on a relatively less severe destruction of hepatic parenchyma, but on the capacity of the hepatic cells to regenerate. The clinical course of the disease is frequently impossible of pathologic correlation, owing to the somewhat latent appearance of the clinical manifestations; however, in a general way the disease exhibits gradations in symptomatic severity and duration similar to those suggested by the pathologic anatomy of

the liver. The most constant symptom presented in these cases is jaundice. Ascites is somewhat latent in its development, but is usually shown when the lesion has reached chronicity. The occurrence of pain in the course of this disease, simulating colic originating in obstruction from biliary calculi, has been emphasized. By far the greater number of patients live to reach the clinically and anatomically subacute and early chronic stages. Death from acute hepatic atrophy, so far as pathologic anatomy reveals it to be acute, is exceedingly rare. In some cases, the end or healed stages of the lesion is reached; this stage presents the characteristics of the type of cirrhosis that Mallory has designated "toxic cirrhosis."

OSTEOGENIC SARCOMA

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(Concluded from page 659)

PART II: THE FIBRO-OSSEOUS FORMS OF OSTEOGENIC SARCOMA

Ossifying connective tissue is of two types, that which ossifies in the wake of calcified cartilage and that which forms bone of the membranous type independently and directly. While these two forms of ossification have long been recognized by embryologists, it is erroneous to assume that the formation of membranous bone is restricted to a few flat bones of the skull and that so-called intracartilaginous ossification (bone in the wake of the cartilage) is the uniform rule in the long bones. It is true that the cancellous portion of the long bones is produced by a more primitive ossification which is dependent on a previous storage of calcium in cartilage. But it is likewise true that in the appendicular skeleton a rim of compact cortical bone is formed directly by a more highly differentiated connective tissue after the perichondrium has been transformed into periosteum of the adult type, and this periosteum in its active portions retains throughout life the power to direct osseous formation.

In the osteogenic sarcomas of fibro-osseous origin it is necessary to distinguish between the form of sarcoma that is related to the function of production of cancellous bone, and is therefore clinically a central sarcoma of bone, and the form of osteogenic tumor that is related to the function of formation of cortical bone and is clinically a periosteal ossifying growth. The first form of neoplasm, which arises most frequently in the cancellous portions of the long bones, is osteolytic and a more primitive tumor than the periosteal sarcoma of the sclerosing type, which arises from the osteogenic layers of the periosteum.

THE OSTEOLYTIC FORM OF OSTEOGENIC SARCOMA

The osteolytic or earlier fibro-osseous form of osteogenic sarcoma is not frequently described as a separate entity, although it has long been recognized as a source of confusion in the diagnosis of tumors of the bone. In the older treatises on pathology, from the time of Virchow up until about 1910, this form of tumor was either referred to as a malignant cyst or aneurysm of the bone, or it was described histo-

logically as an angiosarcoma of the bone. The term "malignant bone aneurysm" can easily be understood if one is familiar with the gross pathologic process of these lesions, since this form of sarcoma is essentially a central destructive growth in which a mass of necrotic bone within the confines of a cortical shell is often replaced by hemorrhagic and vascular tissue. However, as far back as 1876, it was recognized that this was in all probability not a vascular lesion in the bone but a genuine neoplasm of osseous tissue. Sir James Paget,[5] in his lectures on surgical pathology, in 1876, wrote in regard to aneurysms of the bone and the so-called osteo-aneurysms:

> I am far from convinced that, in all the cases thus entitled, the blood vessels of the bone were primarily or chiefly diseased. My impression is that in many of them the disease was really medullary cancer or myeloid tumor of the bone with large development of vessels, and that in some it was such a blood cyst as appears to be sometimes formed in the course of a myeloid or cancerous disease.

Notwithstanding the early origin and the extent of the literature that has accumulated on this subject, this form of sarcoma is rarely recognized in the roentgenogram. Even with the benefit of microscopic examination, competent surgeons and pathologists are repeatedly diagnosing this lesion either as a form of osteitis fibrosa or of giant cell tumor. This mistake accounts for several reports of so-called metastatic giant cell tumors that have recently crept into the literature (Geschickter and Copeland [3]).

Clinical Features.—The clinical features of this osteolytic sarcoma are marked by a wide age distribution, the variability of the region of the bone involved and the frequency of pathologic fracture. The incidence of the disease is maximal, between the ages of 10 and 20, and falls away gradually in the latter decades, but may occur at any age throughout life (fig. 46). Like the other forms of osteogenic sarcoma, the disease is most prevalent in the long bones and most frequently affects the lower end of the femur and the upper end of the tibia. With the exception of pathologic fracture, which occurs in approximately 50 per cent of all cases, the symptomatology of this group of neoplasms is not unique. Trauma is given as the initial event in less than 25 per cent of the lesions, and the usual sequence of symptoms is pain, tumor, limp, trauma and fracture. The average duration of symptoms is slightly under one year prior to the initial treatment (table 4).

As in the other forms of sarcoma of the bone, evidence of a systemic reaction in the form of fever and leukocytosis may be observed at any time during the clinical course. The temperature may range between 99 and 102 F., and the leukocytosis from 11,500 to 17,000. The regional lymph nodes may be enlarged, and in one instance metastatic involvement was microscopically proved.

TABLE 4.—*Osteogenic, Osteolytic Sarcoma*

P. N.	Race, Sex and Age			Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
42844	W	F	20	Femur, lower	3	Pain, tumor six weeks	Destruction in condyle, translucent periosteal shadow	Amputation, September, 1929	Early osteolytic	Metastases to chest 6 mos. later
42614	(Monkey)			Radius, head	..	Pain, tumor	Osseous destruction	Amputation	Mixed, spindle and round cells with giant cells	Dead
42418	W	F	16	Tibia, upper	½	Tumor	Resembling osteomyelitis	Incision and drainage, November, 1929; excision, November, 1929; curettement, December, 1929; curettement, May, 1930	.....	Recurrence; well 2 mos. after last operation
41564	W	F	14	Ilium, right	2	Tenderness, limp	Osteolytic zone	X-ray, April, 1929	.....	Dead
41194	W	M	12	Tibia, upper left	12	Trauma, fluctuating tumor	Subcortical, expanded osteolytic	Curettement, December, 1928; amputation	Large spindle cells, pleomorphic osteoblasts	Well 16 mos. after curettement
40913	W	M	33	Humerus, upper	..	Pathologic fracture	.....	Amputation, March 9, 1927	.....	.....
40768	W	M	49	Femur, lower right	24	Pain, trauma, pathologic fracture	Osseous destruction perforation of shell, some formation of bone	Exploration, March 24, 1917; amputation, Jan. 21, 1925	Large spindle cells, pleomorphic osteoblasts	Dead 1 yr. after operation
40766	W	M	34	Tibia, upper left	12	Trauma, pain, swelling	Involvement of knee joint, destruction, some osseous formation; bone shell of tibia gone	Curettement, 1917; curettement, 1919; amputation, 1921	Mixed, round and spindle cells with giant cells	Dead November, 1922
40526	W	M	12	Tibia, mid-portion	½	Trauma, swelling, pain	Sclerosing periosteal	Curettement, April 4, 1928; amputation, June, 1928	Large spindle cells; pleomorphic osteoblasts; giant cells	Lost
40440	W	M	..	Humerus, upper	5	Pain, tenderness	Mottled slight destruction	Excision of gland, March, 1928	.....	Dead 3 mos. later; autopsy, general metastases
39970	W	M	35	Femur, upper	7	Pain since September, 1926, limp	Mottled slight destruction	Operation advised against	.....	Dead December, 1928
39614	W	M	58	Humerus, upper right	6	Pain, tumor	Osseous destruction, soft part shadow	Amputation, Sept. 30, 1927	Malignant spindle cells, a few osteoblasts	Dead 7 mos. later
39278	W	M	22	Humerus, upper left	....	.....	Osseous destruction with a little formation of bone; large soft part shadow, metastases to chest (?)	Amputation, June 3, 1927	Large spindle cells, pleomorphic osteoblasts	Dead 70 days later
39254	W	F	15	Femur, lower left	4½	Pain, trauma	Osseous destruction, right angle formation of bone	Biopsy, May, 1927	Large spindle cells, pleomorphic osteoblasts, many giant cells	Dead 2½ yrs. later

39026	W	M	19	Humerus, upper left	8	Trauma, pain, tumor	.....	.....	.....	Dead 6 wks. after examination
38882	W	F	17	Tibia, upper right	....	.....	Much osseous destruction, right angle formation of bone	Resection, June, 1927	.....	Well 29 mos. later
38870	W	F	16	Humerus, upper left	3	Trauma, pain, tumor, fracture	Osseous destruction, right angle formation of bone; soft part shadow	Amputation, Feb. 2, 1927	Malignant spindle cells, osteoblasts; a few giant cells	Dead 5 mos. later
38226	C	M	78	Fibula, lower left	9	Pain, tumor	Osseous destruction, formation of bone, periosteal reaction	Amputation, July 24, 1926	Malignant spindle cells, osteoblasts	Lost
38218	W	M	72	Femur, lower	6	Pain, swelling	Central cyst, roughened cortex	Amputation, July, 1926	.....	Dead 5 mos. later
38182	W	F	46	Femur	..	.....	Osseous destruction, formation of bone	Amputation, July 14, 1926	Many malignant spindle cells, a few pleomorphic osteoblasts	Well 9 mos. later
37614	W	F	45	Femur, shaft, right	5	Pain, fracture	Osseous destruction	Amputation, March 25, 1927; curettement, Jan. 25, 1926	Malignant spindle cells, a few osteoblasts	Recurrence after curettement; dead 11 mos. after amputation
37516	W	M	61	Tibia, mid-part, right	..	Pathologic fracture	Pathologic fracture, excess callous	Amputation advised	.....	Well June, 1930
37008	W	M	15	Femur, lower left	2	Trauma, tumor	Periosteal reaction with osseous formation and destruction, soft part shadow	Exploration 4 times in two months, amputation, Aug. 30, 1925	Malignant spindle cells; pleomorphic osteoblasts	.....
36724	W	F	10	Tibia, lower shaft, right	8	Pain, tumor	Osseous destruction and expansion with cystic areas	Exploration, 1924; amputation advised, 1925	Pleomorphic osteoblasts	Dead
36456	W	M	39	Femur, upper shaft, right	9½	Trauma, pain, pathologic fracture	Osseous formation and destruction with expansion involving the shaft, radiating bone	Preoperative radiation; amputation, April 24, 1925	Malignant spindle cells and pleomorphic osteoblasts	Well 3 yrs., now dead
35786	W	M	15	Femur, lower	11	Trauma, repeated; tumor	.....	Amputation	Malignant spindle cells, pleomorphic osteoblasts, osteoid tissue	Dead 5 mos. later
35212	W	M	20	Fibula, lower	36	Tumor, pain	Destruction, periosteal roughening	Exploration, April 21, 1924; amputation, May 10, 1924	.....	Dead 1 yr. later
35088	W	M	24	Humerus, upper right	2	Pain, swelling	Mottled-periosteal lipping	X-ray, December, 1923	.....	Dead 1 yr. later
34536	W	F	24	Femur, lower right	6	Trauma, pain, swelling	Osteoporosis, formation of bone	Amputation, Dec. 1, 1922	.....	Dead 4 mos. later
34532	W	M	30	Tibia, upper right	3	Swelling, pain	Osteoporosis and destruction	Amputation, June 2, 1923	Mixed, spindle and round cells	Dying with metastases, Sept. 12, 1924
34420	W	M	18	Tibia, shaft, upper	12	Trauma, pain, tumor	.....	Amputation, Dec. 13, 1923	Malignant spindle cells	Well 1 yr., 4 mos., lost
34334	W	M	12	Femur, lower	12	Pain, swelling	Central destruction, onion-peel periosteal appearance	Curettement, Nov. 23, 1923	Malignant spindle cells, pleomorphic osteoblasts, much osteoid material	Dead 1 yr., 2 mos. later
34070*	W	F	15	Humerus, upper	3	Pain, swelling	Destruction, raised periosteum	X-ray; amputation, August, 1923	.....	Dead 4 mos. later
33928	W	M	46	Femur, lower shaft	4	Pain, pathologic fracture	.....	Exploration, Sept. 11, 1923; amputation, Sept. 23, 1923	.....	Dead 1 yr., 3 mos. later

TABLE 4.—*Osteogenic, Osteolytic Sarcoma—Continued*

P.N.	Race, Sex and Age			Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
33512	W	M	11	Femur, lower right	1	Trauma, pain, pathologic fracture	.....	Exploration, Feb. 4, 1923; irradiation, April 23, 1923; amputation, May, 1923	Malignant spindle cells, pleomorphic osteoblasts with giant cells	Dead 6 mos. after amputation
32908	W	F	..	Femur, lower	..	.....	Resembling giant cell tumor	Amputation, December, 1921	Mixed, spindle and round cells with giant cells	Recurrence; dead 10 mos. later
32663	W	M	20	Humerus, upper	4	Pain, trauma, fracture	.....	Exploration, Dec. 6, 1922; amputation, April, 17, 1922	Malignant spindle cells, pleomorphic osteoblasts	Dead 5 yrs., 2 mos. later
32278	W	M	30	Humerus, lower	1	Trauma, pain, tumor	Destruction, roughened periosteum	Incision, Nov. 19, 1922; amputation, Dec. 13, 1922	.....	Dead 10 mos. later
32093*	W	M	14	Tibia, upper right	1	Trauma, pain, tumor	.....	Curettement, June, 1920; amputation, July, 1920	Malignant spindle cells, pleomorphic osteoblasts with giant cells	Dead 4 mos. later
31890	W	M	35	Tibia, lower	7	Pain, tumor	Central destruction	Curettement, 1908; amputation, 1909	Mixed spindle and round cells, with giant cells	Dead 7 yrs. later
31695	W	F	16	Femur, mid-part	1½	Pain, swelling	Osseous destruction with roughened periosteum	.....	.....	Dead
31383	W	F	16	Femur, lower shaft	5	Pain, tumor	.....	Curettement, August, 1922; irradiation; amputation, Jan. 6, 1923	Malignant spindle cells, pleomorphic osteoblasts with osteoid material	Dead 3 yrs., 11 mos. later
30189	C	F	20	Tibia, mid-part	3	Swelling, pain, pathologic fracture	Diffuse destruction, some osseous formation	Excision, Aug. 4, 1921; amputation, Aug. 5, 1921	.....	Dead 2 mos. later
29400	W	M	32	Femur, lower left	16	Pain, tumor	.....	Exploration, Jan. 6, 1922; amputation, Jan. 10, 1922	Malignant spindle cells, pleomorphic osteoblasts	Dead almost 3 yrs. later
29363	W	M	21	Femur, lower right	4	Trauma, pain, swelling	Destruction of bone shell	Excision, Feb. 4, 1921; curettement, March 5, 1921; amputation, April 30, 1921	Large spindle cells, pleomorphic osteoblasts	Dead 4 mos. after amputation
29362	W	F	67	Femur, lower right	6	Pain, swelling, pathologic fracture	Great destruction	Amputation, July 12, 1921	Large spindle cells, pleomorphic osteoblasts	Dead 1 mo. later
29361	W	M	27	Ischium	24	Trauma, swelling	Destruction of ischial ramus	Curettement, March 21	Large spindle cells, pleomorphic osteoblasts	Dead almost 2 yrs. later
29084	W	M	56	Femur, upper left	4	Pain	Osseous destruction and onion-peel formation	Exploration, Oct. 29, 1921; amputation, June, 1924	.....	Dead
28925	W	F	14	Tibia, upper	2	Pain, tumor	.....	Amputation, October, 1921, after curettement, August, 1921	Malignant spindle cells, pleomorphic osteoblasts, infection	Dead 4 mos. after amputation
28574	W	F	49	Femur, lower	12	Pain, tumor, pathologic fracture	Extensive destruction	Amputation, March 17, 1921	Malignant spindle cells, pleomorphic osteoblasts, giant cells, old bone	Dead of operation

28402	W	F	..	Tibia, right	..	.....	Central lesion	Curettement, Nov. 26, 1917; irradiation (postoperatively), amputation, Oct. 17, 1918	.....	Dead 3 yrs. after amputation
28277	W	M	50	Femur, head	..	.....	Destruction of acetabulum, head and neck of femur	Exploration, Coley's toxins	Malignant spindle cells, pleomorphic osteoblasts	Lost
28248	...	F	..	Tibia, upper	..	.....	Central osseous destruction, slight formation of bone, periosteal reaction	Amputation, 1917	.....	Dead 5 yrs. later
27938	W	M	69	Frontal bone	1½	Deafness, no definite trauma	Skull defect in frontal bone	Excision, February, 1921	Mixed, spindle and round cells	Dead 2 mos. after operation
27908	C	M	43	Tibia, lower	18	Trauma, tumor, pathologic fracture	.....	Amputaton, April 8, 1921	Malignant spindle cells, pleomorphic osteoblasts	Well 6 yrs. later
27890	W	M	..	Femur, lower	22	Fracture, December, 1919	Central tumor with expansion and periosteal reaction	Amputation, Feb. 4, 1921	Mixed, spindle and round cells	Dead 1 yr., 7 mos. later
27852	W	F	17	Femur, lower	3	Pain, tumor	.....	Exploration, March 18, 1921; amputation, May 19, 1921; preoperative irradiation, July 27, 1921	Malignant spindle cells, pleomorphic osteoblasts	Dead 3 mos. after amputation
27848	W	M	19	Radius, lower	5	Pain, tumor	.....	Toxins, preoperative irradiation; amputation arm; excision of pectoral muscles and glands, June 22, 1921	.....	Dead same year
27290	W	F	26	Humerus, upper	..	Tumor, pathologic fracture	.....	Resection twice, April, 1901; exploration, June 5, 1901; amputation, June 7, 1901	Malignant spindle cells, pleomorphic osteoblasts	Alive 3 yrs. after operation, lost
26919	...	F	55	Femur, lower, tibia, upper, fibula	24	Trauma, 2 yrs., tumor, second trauma	.....	Amputation, August, 1920	Mixed, round and spindle cells	Dead 4 mos. later
26877	W	M	30	Tibia, upper	48	Pain, tumor	.....	Exploration, January, 1917, followed by Neisser's serum; exploration, August, 1920; amputation, Dec. 22, 1920	Round and spindle cells	Well nearly 9 yrs. after amputation
26855	W	F	14	Tibia, upper left	½	Pain, tumor	.....	Curettement, September, 1920; amputation, October, 1920; cauterization, June, 1920	Large round cells with giant molar nuclear cells	Dead 10 mos. after amputation
26709	W	M	19	Femur, lower	..	Tumor, trauma	.....	Exploration, May 22, 1909; excision, July 4, 1909; amputation, Aug. 5, 1909	Large round cells with giant cells	Well 18 yrs., 4 mos. later
26612	W	M	15	Fibula, upper	3	Pain, tumor, pathologic fracture	Marked osseous bone destruction with pathologic fracture, tumor of soft part and slight formation of bone, cortical expansion	None	.....	Dead
26593	W	M	..	Femur, lower	..	Pathologic fracture	.....	Two amputations	.....	Dead July 16, 1921 from other causes
24966	W	F	12	Femur, lower	2	Trauma, pain, tumor	.....	Amputation, Aug. 25, 1919	Malignant spindle cells, pleomorphic osteoblasts, osteoid tissue	Dead 6 mos. later
23101	W	F	20	Femur, lower left	48	Tumor, trauma	.....	Preoperative irradiation, excision, May 5, 1918; amputation, June 6, 1918	.....	Dead 3 yrs., 5 mos. later
22109½	W	F	..	Femur, lower	..	.....	Destruction of lower end of femur; repair of fracture	Amputation and Coley's toxin, July 3, 1918	.....	Dead 3 mos. later
16934	W	M	18	Humerus, upper right	5	Trauma 5 mos., tumor 1 mo.	.....	Amputation, Feb. 9, 1915	Large spindle cells, pleomorphic osteoblasts	Dead 2 mos. later

TABLE 4.—*Osteogenic, Osteolytic Sarcoma—Continued*

P. N.	Race	Sex	Age	Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
16571	W	M	21	Femur, midpart	2	Trauma, pain, tumor	.....	Exploration, Nov. 19, 1914; amputation, Dec. 2, 1914	Malignant spindle cells, pleomorphic osteoblasts; giant cells	Dead 5½ mos. later
16158	W	M	16	Tibia, upper	2	Tumor	Osseous destruction, periosteal roughening	Exploration, Jan. 8, 1913; excision, upper third of tibia, Jan. 13, 1913; amputation at thigh, August, 1914	Mixed spindle cells, pleomorphic osteoblasts with giant cells	Dead 1 yr. later
15404½	W	F	18	Tibia	4	Trauma with repaired fracture	.....	Incision; amputation, Jan. 14, 1914	Malignant spindle cells, pleomorphic osteoblasts	Dead from operation
14229	W	F	35	Femur, lower	..	.....	Central destruction (aneurysm)	Amputation, June 2, 1913	Mixed spindle and round cells, pleomorphic osteoblasts, giant cells	Dead 11 yrs. later
13092	W	M	39	Tibia, upper	24	Trauma, pain, tumor	Central destruction	Curettement, Aug. 8, 1912; toxins and amputation, Sept. 19, 1912	Mixed spindle and round cells	Dead 7 mos. later
12050	W	M	26	Femur, lower	5	Pain, tumor	.....	Exploration, Jan. 7, 1911; amputation, Sept. 29, 1911	Mixed spindle and round cells	Dead 8 days after amputation, (toxemia)
11252	W	M	60	Humerus, upper	17	Tumor, pathologic fracture, trauma, pain	.....	Amputation, July 25, 1911	Mixed spindle and round cells	Dead 6 mos. later
10868	W	F	12	Femur, lower	2	Pain, swelling	.....	Coley's toxin; curettement, Sept. 27, 1910	Large round cells	Dead 4 mos. later
10602	W	M	30	Humerus, shaft	24	Pain, trauma, pathologic fracture	Central destruction	Curettement, Aug. 23, 1910; curettement, Oct. 10, 1910; amputation, April, 1912	Mixed spindle and round cells, osteoid substance, giant cells	Dead 4½ yrs. later amputation
9725	W	F	12	Femur, lower	..	.....	.....	Amputation, May 31, 1909	Malignant spindle cells, pleomorphic osteoblasts, a few giant cells	Dead 2 yrs. later
9397	W	M	15	Tibia, head and shaft	2	Pain, tumor	.....	Curettement; amputation, 10 days later	Mixed spindle and round cells	Dead 3 mos. later
9073	W	M	24	Ulna, upper	20	Tumor	.....	Resection, May 13, 1907	Spindle cells, giant cells	Dead 2 yrs. later
8182	W	M	41	Femur, upper left	18	Limp, tumor	Osseous destruction	Exploration, May 8, 1907	.....	Lost
7964	W	F	17	Fibula, upper	9	Pathologic fracture, tumor, pain	Complete destruction	Amputation, 1904	Malignant spindle cells, pleomorphic osteoblasts with giant cells	Dead 9 mos. later
6430	C	M	13	Femur, lower	..	Pain, tumor	.....	Exploration, May 29, 1905; amputation, July 6, 1905	Malignant spindle cells, pleomorphic osteoblasts	Lost
3850	W	F	48	Tibia, upper	24	Pain, tumor	.....	Exploration; amputation, 1901	Malignant spindle cells, pleomorphic osteoblasts, giant cells	Well 2 yrs., lost
3231	W	M	39	Tibia, upper	11	Pain, tumor, pathologic fracture	.....	Amputation, Aug. 10, 1900	Malignant spindle cells, pleomorphic osteoblasts, with giant cells	Dead 2½ mos. later
2481	W	F	16	Tibia, upper right	5	Pain, tumor, repaired fracture	.....	Exploration and amputation, 1899	Mixed spindle and round cells with giant cells	Dead 6 mos. later (pulmonary metastases and recurrence in stomach)
313	W	M	22	Femur, lower	7	Pain, tumor	Osseous destruction	Exploration, Feb., 1899; amputation, May, 1899	Mixed round and spindle cells	Dead 5 mos. after amputation

The usual point of origin of these growths is in the subcortical region of the metaphysis. The lesion, however, rapidly invades cancellous bone and the medullary spaces so that when examination is delayed the diseased area extends to a more central location, and the epiphysis or the shaft is involved. Once the new growth has reached the epiphysis, destruction of the bone is sufficiently advanced to create the typical vascular cavity suggestive of an aneurysm of the bone, and pulsation with symptoms referable to the joint may occur.

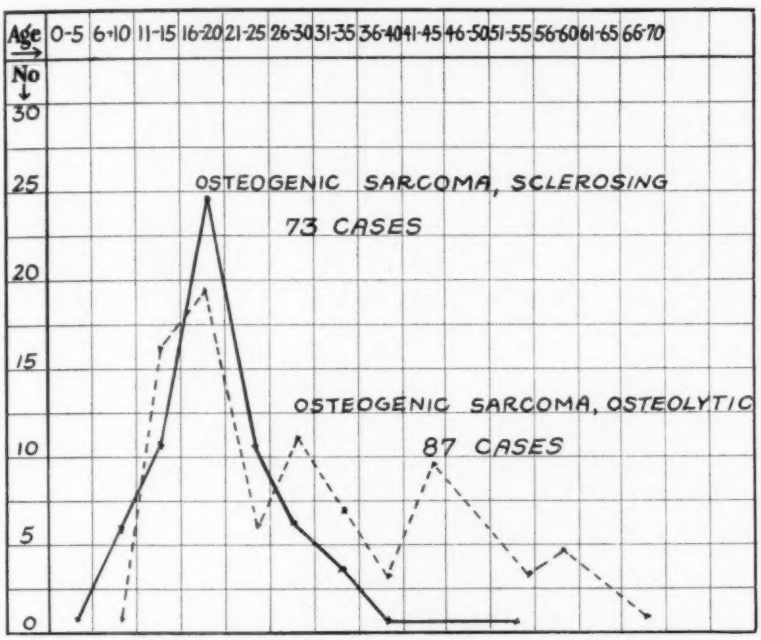

Fig. 46.—Chart showing the comparative age distribution of osteolytic (dotted line) and sclerosing (solid line) osteogenic sarcoma.

Examination of the affected limb reveals a swelling over which the skin is movable but tense, without much reddening (figs. 47, 48, 49 and 50). The superficial veins may or may not be dilated, depending on the size of the growth. On palpation, the peculiarity of these tumors is their boggy feeling and the slight suggestion of a semifluctuant nature. Pulsation, when present, immediately brings to mind the old clinical entity of the malignant aneurysm of the bone. Limitation may occur in the adjacent joint, but excess fluid in the joint cavity or actual involvement of the joint rarely occurs. In half of these cases an ununited pathologic fracture is present.

Figs. 47-50 (P. N. 39278).—A case of osteolytic sarcoma of the upper end of the humerus occurring in a white man, aged 22, who died two months after a primary amputation. This figure (fig. 47) shows the large boggy swelling over the upper end of the humerus characteristic of this type of neoplasm referred to in the old literature as malignant aneurysm of the bone.

Fig. 48 (P. N. 39278).—Roentgenogram of the lesion. The upper end of the humerus has been replaced by a hemorrhagic mass of neoplastic tissue which has infiltrated into the soft parts.

Roentgenologic Features.—The x-ray films of this osteolytic form of sarcoma of the bone are extremely difficult to interpret. These lesions are confused with benign cyst of the bone, benign giant cell tumor, metastatic carcinoma to bone and Ewing's sarcoma, even by those experienced in roentgenologic diagnosis of lesions of the bone. Among those less experienced, the mistake of confusing this tumor with osteomyelitis is frequent.

Fig. 49 (P. N. 39278).—Gross specimen showing the hemorrhagic character of the neoplasm and its bone-destructive tendencies.

The most important diagnostic feature in the roentgenograms is the central area of irregular destruction of the bone which extends through the unexpanded cortex, resulting in a periosteal reaction. The early and late manifestations of the disease present different diagnostic problems from the roentgen standpoint.

In the early cases (figs. 51, 52, 53 and 55) the area of osseous destruction is subcortical and metaphyseal and slightly expands the overlying shell of cortical bone, thinning it and causing perforation or a melting away in one or more directions. The youthful age of the

patient, the osteolytic, central and metaphyseal character of the lesion immediately suggest the possibility of a benign cyst of the bone. The distinguishing features in the x-ray film, however, are the melting away and perforation of the bone shell at an early stage in the history of the disease at the time when the area of destruction is still asymmetrically located, the presence of a periosteal reaction and the slight degree of cortical expansion. In the benign cyst of the bone the bone shell

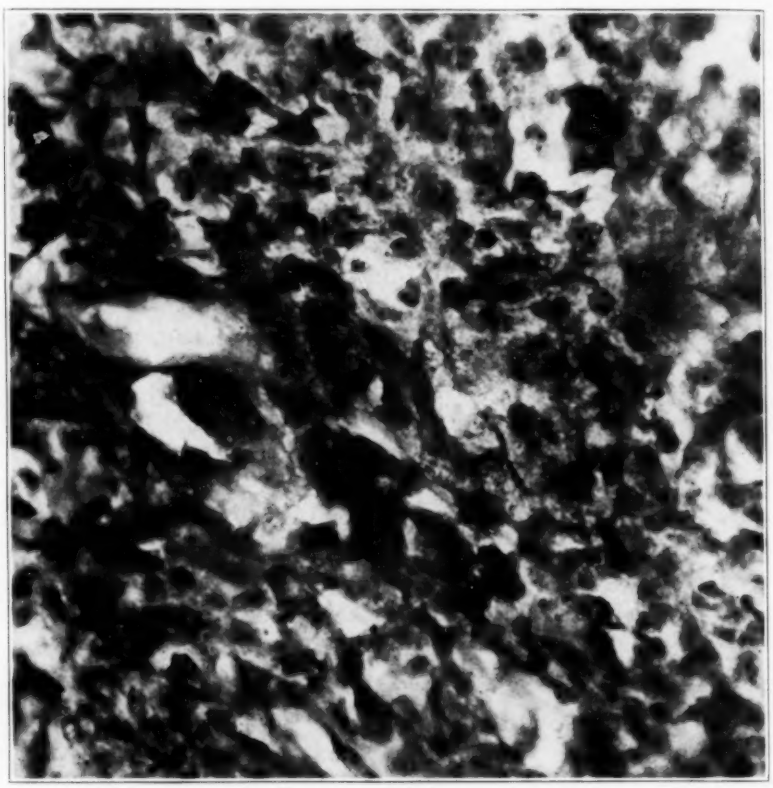

Fig. 50 (P. N. 39278).—High power photomicrograph of the tissue which is a mixture of malignant spindle and abortive osteoblasts. The large pleomorphic tumor cells are undergoing necrosis.

is symmetrically expanded, and the area of osseous destruction traverses the whole diameter of the marrow cavity before a pathologic fracture leads to perforation of the bone shell. There is also, in most instances, definite indication of the formation of new bone on the inner border of the expanded cortex, a finding lacking in osteolytic sarcoma (fig. 52).

In advanced cases, the marked osseous destruction and periosteal involvement make the diagnosis of malignancy relatively certain.

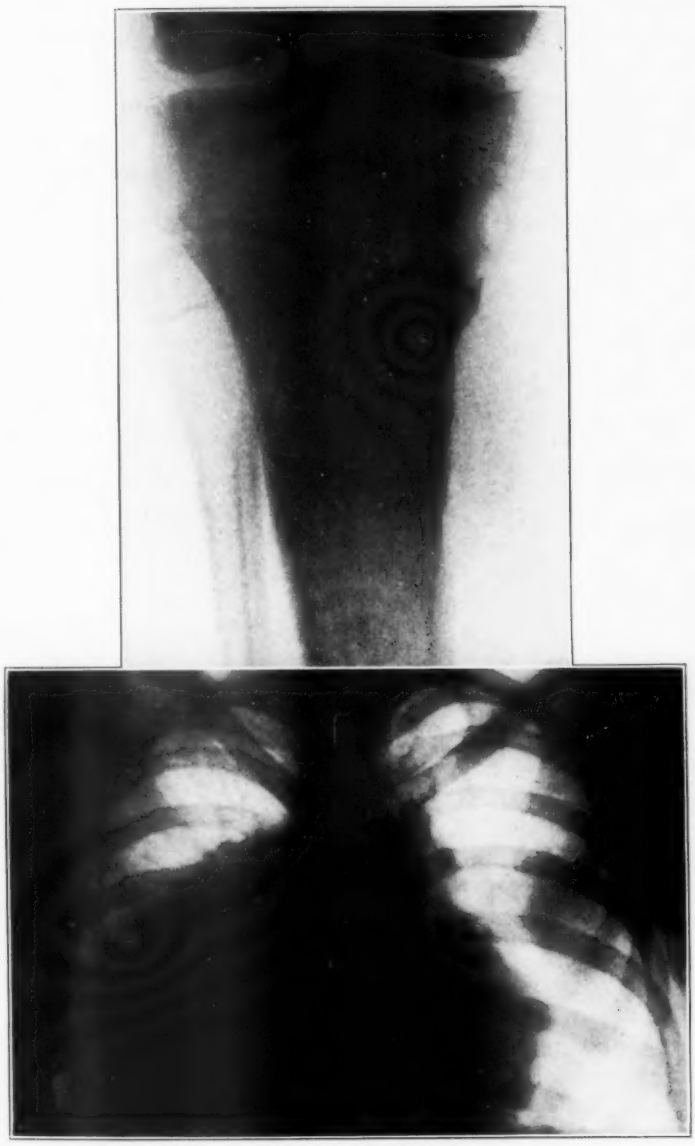

Fig. 51 (P. N. 16158).—Early roentgenogram of a case of osteolytic sarcoma in the upper end of the tibia of a white boy, aged 16, taken two months after the onset of symptoms. The tumor was three times excised before amputation was performed. The patient died one year afterward. A small area of osseous destruction is shown in a subcortical and metaphyseal location perforating the cortex. The roentgenogram of the chest taken shortly before death shows a huge mediastinal mass on the right, overlapping the heart shadow.

Metastatic carcinoma or a focus of multiple myeloma may then be suspected, but the bone has a more splintered and worm-eaten appearance and the degree of invasion into the soft part is far more pronounced in osteolytic sarcoma. Usually the youth of the patient will aid in making the distinction, since carcinoma and multiple myeloma are practically restricted to the years beyond 35, but it must be remembered that this form of sarcoma may also occur in later life.

Fig. 52 (P. N. 41194).—Roentgenogram of an osteolytic sarcoma erroneously diagnosed as a cyst of the bone. The periosteal reaction, the perforation of the bone shell and the absence of osseous expansion led to the correct diagnosis from the roentgenogram in this laboratory.

The more protracted cases of osteolytic sarcoma are puzzling. These occur in adults and are nearly always confused with a benign giant cell tumor. The epiphysis is secondarily invaded by an expansile tumor with a perforated bone shell and a definite periosteal reaction (fig. 57). The metaphyseal portion of the bone is included in the tumorous process, and in several instances the joint cavity has become secondarily involved due to erosion or splitting of the articular cartilage. The history given

by the patient may extend over a period of from three to six years, and an operation, including exploration and biopsy, is necessary to rule out a benign giant cell growth. Cases of this type have been reported by Goforth,[28] Finch and Gleave,[29] Chatterton and Flagstad,[30] and others as metastatic giant cell tumor when the patients ultimately succumbed to metastases. A similar case recorded by Bloodgood [31] as an authentic cure by amputation in this type of sarcoma has been classified by mem-

Fig. 53 (P. N. 41194).—Lateral view of the tumor shown in figure 52. This view emphasizes the similarity of the roentgenogram to a benign cyst of the bone.

bers of the Bone Registry as giant cell tumor, and its malignant nature doubted (figs. 58 and 59).

28. Goforth, J. L.: Giant Cell Tumor of Bone, Arch. Surg. **13**:846 (Dec.) 1926.

29. Finch, E. F., and Gleave, H. H.: A Case of Osteoclastoma with Pulmonary Metastases, J. Path. & Bact. **29**:399, 1926.

30. Chatterton, C. C., and Flagstad, A. E.: J. Bone & Joint Surg. **9**:113, 1927.

31. Bloodgood, J. C.: The Diagnosis and Treatment of Benign and Malignant Tumors of Bone, J. Radiology **1**:147, 1920.

The final status of these growths rests on a microscopic analysis and will be discussed in more detail subsequently when the histogenesis of this osteolytic form of sarcoma is considered.

Gross Pathology.—At exploration, a vascular tumorous mass may be found in the soft parts confined by muscle and fascia only. More

Fig. 54 (P. N. 41194).—High power photomicrograph showing the extreme anaplastic properties of the tumor cell. Note the mitotic figure of the cell in the center of the field. (Same case shown in figures 52 and 53.)

commonly the tumor is beneath the periosteum with the bulk of the neoplastic tissue within a shell of cortical bone. Vascularity is the rule, and a mass resembling a blood clot or active hemorrhage may be

encountered (figs. 49 and 59). In one case (fig. 60) an exploratory incision, made under the impression that an abscess was present, released a severe hemorrhage which resulted in a marked anemia, and in most instances in which the operation opens up the medullary spaces of the cancellous bone profuse bleeding occurs.

The neoplastic mass is soft and friable and usually resembles the blood-stained tissue seen in giant cell tumor. More fibrous areas, white

Fig. 55 (P. N. 36724).—An osteolytic sarcoma occurring in a boy aged 10, who died of metastases despite an early operation. The appearance in the roentgenogram is not unlike that of a cyst of the bone, except that the areas of destruction are asymmetrically located and have extended up and down the shaft of the bone rather than across the medullary cavity.

and firm, are usually to be found, and where this more consistent material predominates, secondary hemorrhagic cysts are enclosed by it.

Amputated specimens show a mixture of fibrous and hemorrhagic tumor tissue permeating the marrow cavity, rupturing the cortex and spreading subperiosteally and into the soft parts. The site of the tumor

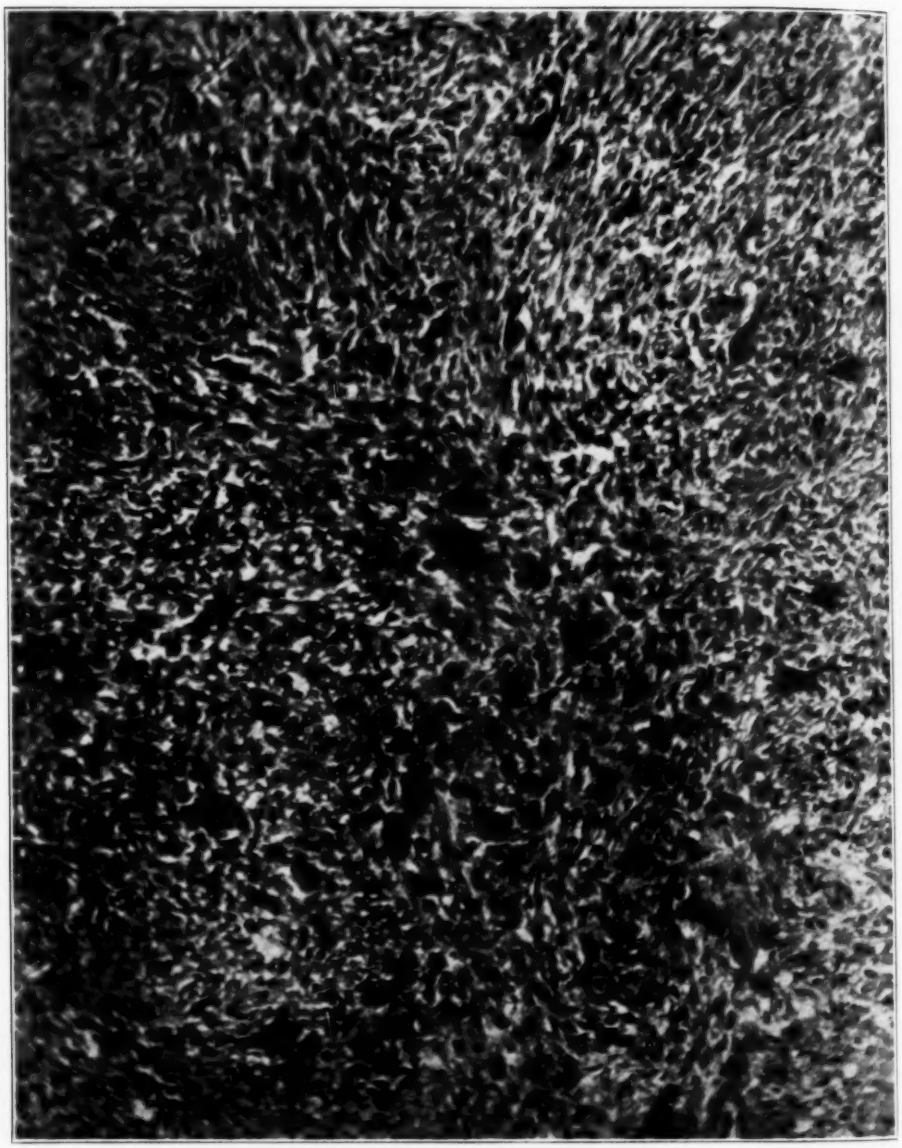

Fig. 56 (P. N. 36724).—Photomicrograph of lesion shown in figure 55, showing early osteoblasts and metaphyseal location and a definite periosteal reaction.

is practically always to the shaft side of the epiphysis, and at this point the shaft is usually fractured transversely. In early cases the cancellous bone in the medullary cavity is rapidly destroyed, and the cortex perforated at one or two points rather than melted away. This destruction in the medullary cavity seems to proceed rapidly until the cortex is ruptured and the pressure within the bone shell relieved, after which the tumor proliferates into the less resistant soft parts. However, with

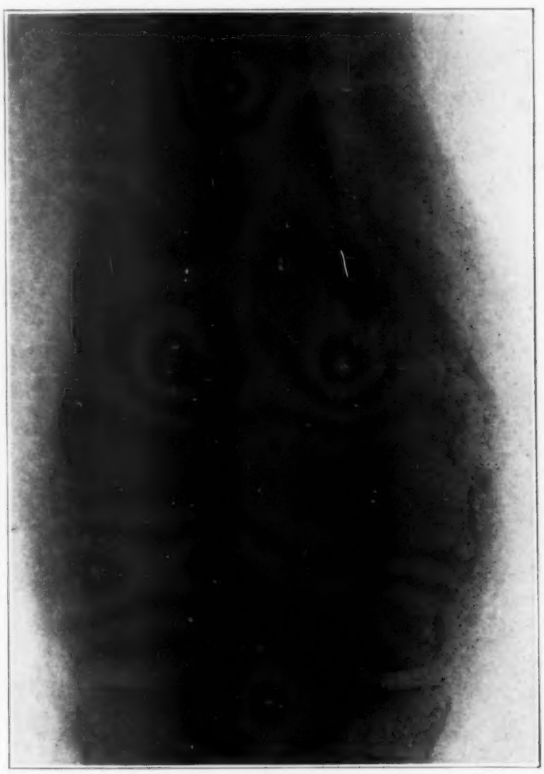

Fig. 57 (P. N. 40874).—A secondary osteolytic sarcoma reported by Chatterton and Flagstad (*J. Bone & Joint Surg.* **9**:113 [Jan.] 1927) as a metastatic giant cell tumor, occurring in a white woman, aged 30, who died eight years after the initial symptoms with pulmonary metastases. The roentgenogram depicts the unusual amount of osseous expansion caused by the tumor, which has invaded the epiphysis.

the continued growth of the tumor, which now advances with less devastating effect under released pressure in the medullary cavity, the cancellous bone is capable of partial defense and reacts with slight sclerosis.

The central origin of the tumor, prior to its escape into the soft parts, is evident in the specimens by the fact that tumor perforates into the subperiosteal zones often in diametrically opposed directions. In advanced cases the entire shaft of the bone may be displaced with a white fibrous tumor tissue dotted here and there with hemorrhagic cysts (figs. 60 and 61).

Microscopic Features.—The microscopic sections account for the extreme vascularity of the tumor. Blood spaces usually without

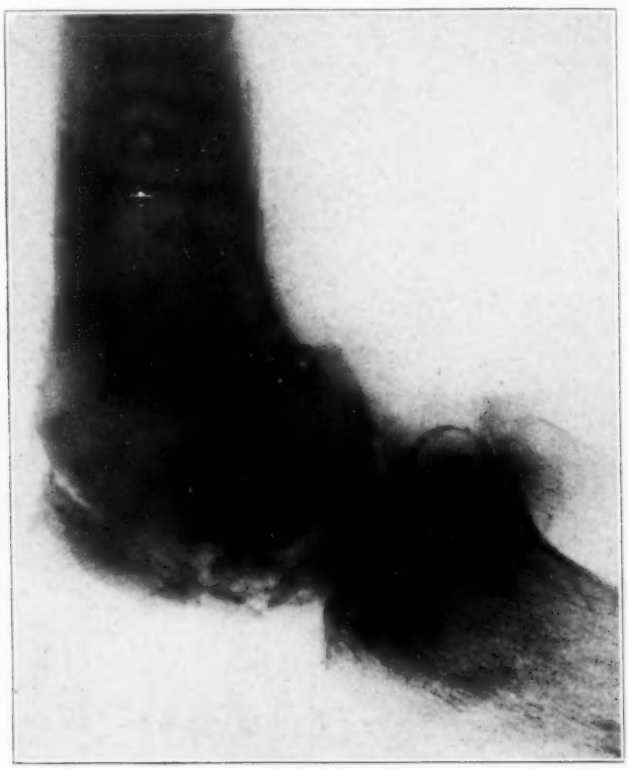

Fig. 58 (P. N. 14229).—An osteolytic sarcoma arising secondarily in a woman, aged 61, who was cured by amputation. In the roentgenogram, the sarcoma was differentiated with difficulty from a benign giant cell tumor, but it has a more metaphyseal location and a definite periosteal reaction.

endothelial lining are prevalent in a tissue composed of plump malignant spindle cells and round abortive osteoblasts. One of the marked histologic features is the extreme degree of malignancy or anaplasia shown by the nuclei in cells of the various types. Hyperchromatism and mitotic figures are prominent throughout most of the sections (figs. 54 and 65). A varying amount of osteoid intercellular material can be

demonstrated. Often this preosseous material can be brought out only by special staining methods, but its definite tumorous origin is shown by its occurrence in metastatic pulmonary nodules.

Giant cells of the epulis type are common in the less rapidly growing neoplasms and are replaced by multinucleated tumor giant cells in the more malignant growths. The presence of these giant cells in the sections is often a source of confusion to pathologists, and explains why

Fig. 59 (P. N. 14229).—The gross specimen shown is characteristic of the old pathologic entity of malignant aneurysm of the bone. The microscopic structure of the tumor was typical of an osteolytic form of osteogenic sarcoma. (For roentgenogram see figure 58.)

some of the fatal cases of this form of osteolytic sarcoma have been reported as instances of metastasizing giant cell tumor.

The following are important points in the microscopic differential diagnosis: 1. In the absence of infection, the finding of the malignant plump spindle cells with dusty nuclei is pathognomonic of sarcoma when the specimen under examination has been taken from bone, and particularly when these dusty nuclei are duplicated within the same cell.

2. The large round cells with numerous mitotic figures referred to here as abortive osteoblasts are also characteristic of malignancy (figs. 65 and 66). These two malignant forms of spindle and round cells are common to osteolytic sarcoma in bone and are never found in an uninfected benign giant cell tumor. The benign giant cell tumor may have spindle and round cells in its stroma, but these are small and

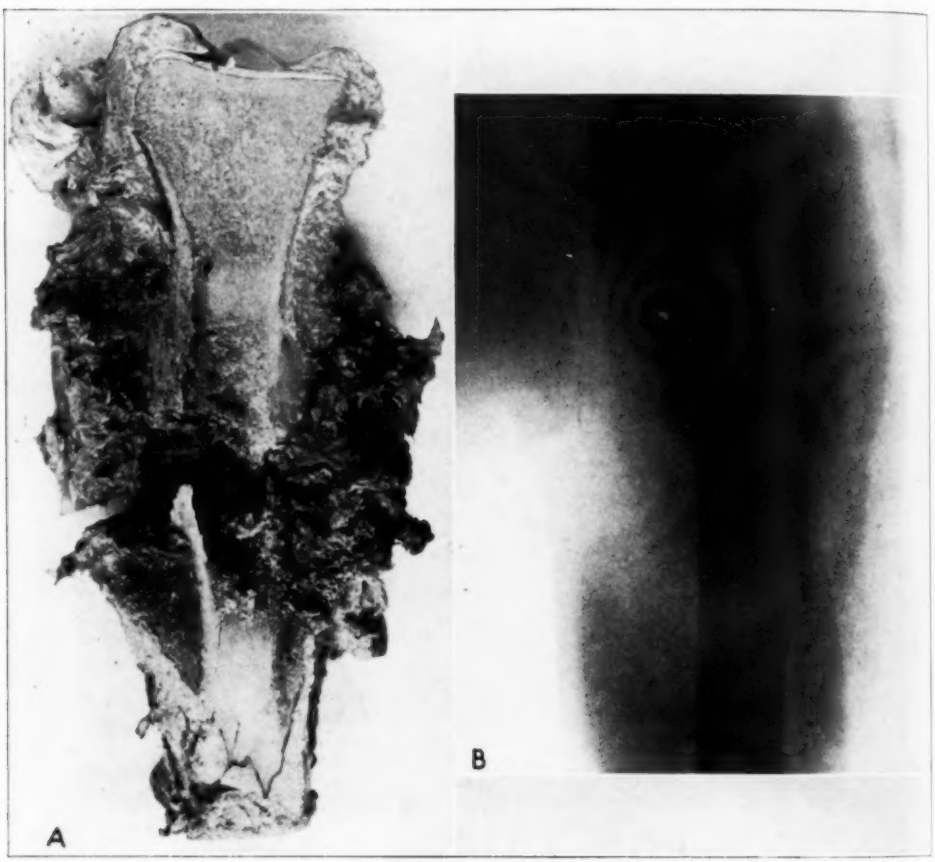

Fig. 60 (P. N. 15404½).—A case of osteolytic sarcoma in a white girl, aged 14, who suffered from pain and swelling of four months' duration in the mid-region of the tibia. *A* shows the characteristic destruction and splintering of the bone with a pathologic fracture. *B* indicates the site of the central vascular cavity which has eroded into the soft parts. An attempt was made to incise the tumor mass in the soft parts of the popliteal space, resulting in a severe hemorrhage. Thirty-six hours later an amputation was performed, and the patient died a few hours afterward.

have not the malignant appearance in their nuclei that is evident in the round and spindle cells just described. 3. Giant cells are sparse in

osteolytic sarcoma and rarely predominate in the section. They are small, usually have less than fifteen nuclei to the cell, and show a tendency to be replaced by giant cells of the malignant tumor type (fig. 67). In benign giant cell tumors the giant cell predominates, and these cells average over fifteen nuclei.

The details of the microscopic appearance of these tumors are best obtained from the photomicrographs shown here. The relative frequency of the occurrence of giant cells in these tumors and the constancy of the findings of the malignant spindle cells or pleomorphic osteoblasts can be judged by consulting the microscopic notes recorded in table 4.

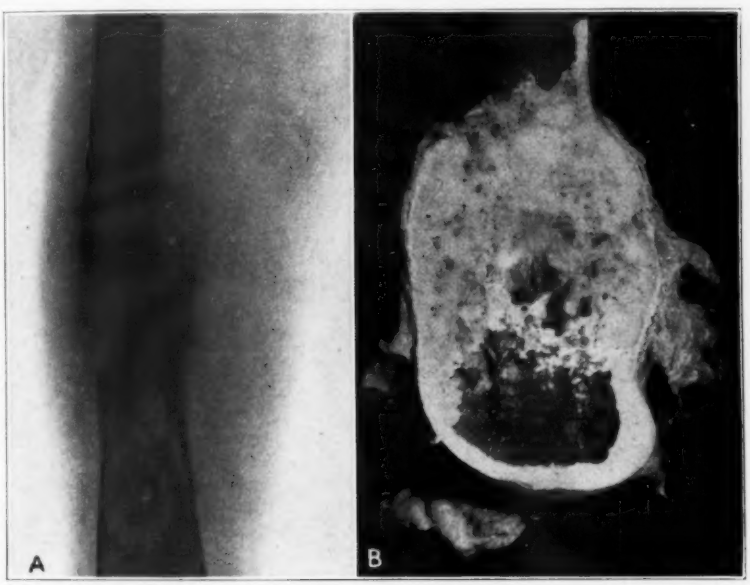

Fig. 61 (P. N. 36456).—A late stage of osteolytic sarcoma simulating metastatic carcinoma. The patient was an adult, aged 39, who died three years after the amputation. *A* shows the destruction of the shaft of the bone by the new growth producing a pathologic fracture. Osseous expansion is not marked, and there are several secondary areas of osseous resorption in the medullary cavity below the lesion. *B* emphasizes the white fibrous nature of the tumor substance invading the shaft above the epiphysis.

It is important to call attention to certain features that set this tumor apart from other forms of sarcoma of the bone. Although in many of the tumors the malignant spindle cell rather than the osteoblasts predominates, this neoplasm can be distinguished from periosteal fibrosarcoma by the fact that the early connective tissue cells do not tend to differentiate into fibroblasts with the whorl formation of fibrillae but

Fig. 62 (P. N. 36456).—Low power photomicrograph showing the central location of the tumor mass depicted in figure 61. The surviving trabeculae of cortical bone are enclosing the neoplastic tissue.

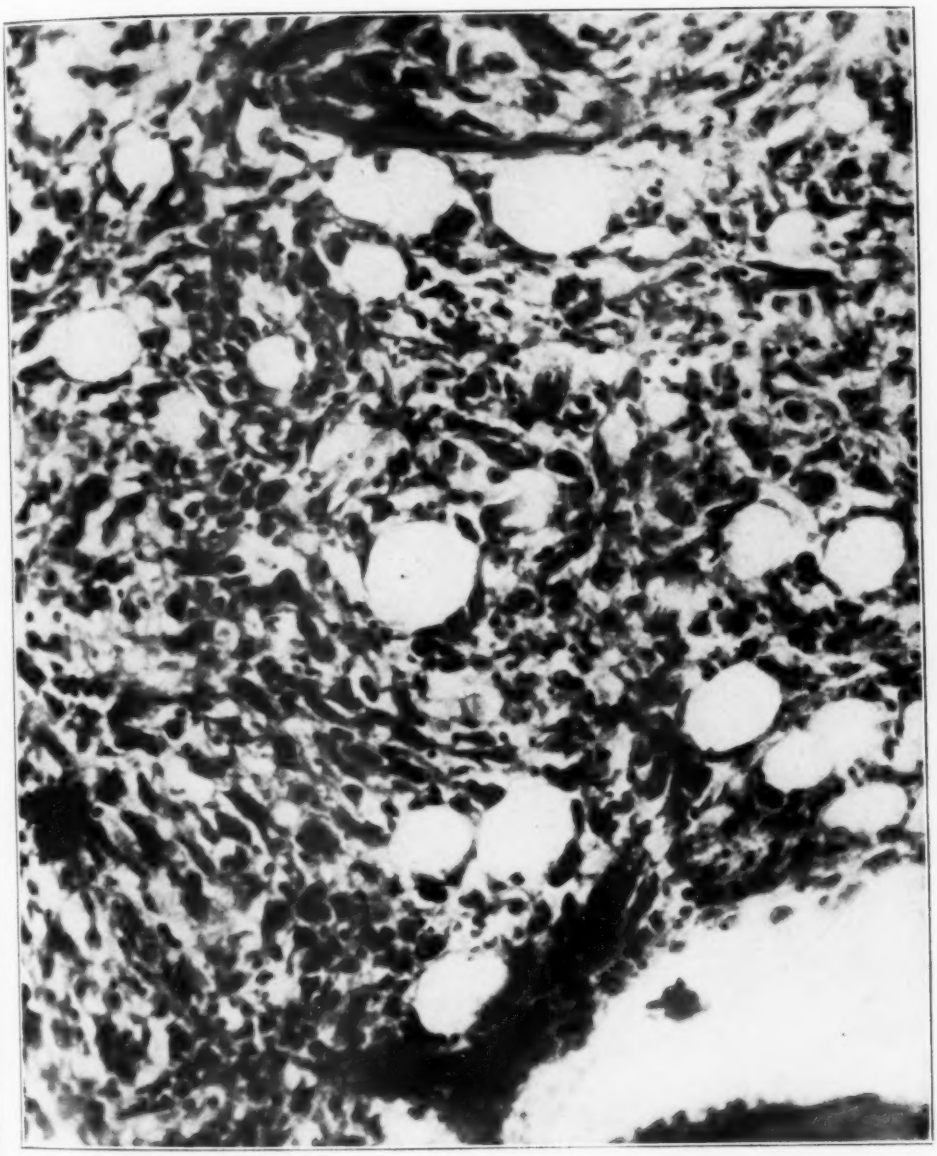

Fig. 63 (P. N. 36456).—High power photomicrograph of the tumor shown in figures 61 and 62. Malignant spindle cells and osteoblasts are invading the fatty bone marrow.

instead are converted into the osteoblasts of the type described. The small amounts of osteoid substance produced is not seen in fibrosarcoma.

Osteolytic sarcoma is distinguished microscopically from the sclerosing form by the sparsity of the osseous substance produced, and by the

Fig. 64 (P. N. 28574).—Photomicrograph showing the formation of blood spaces rimmed by giant cells found in the vascular areas of osteolytic sarcoma.

fact that the osteoblasts, instead of associating themselves with irregular spicules of newly formed bone, tend to show extreme signs of anaplasia and lie free in a stroma of spindle cells. There is, however, a slight overlap, microscopically, in an occasional case of the so-called

early sclerosing type, which will be discussed under sclerosing osteogenic sarcoma.

Differentiation of this type of sarcoma from the chondral forms is easily made by means of the microscope, as both calcifying cartilage, such as is seen in chondroblastic sarcoma, and myxoma and fetal cartilage, such as is seen in chondrosarcoma, are lacking.

The interpretation of this osteolytic neoplasm as an angiosarcoma is ruled out by the definite signs of ossification of tumorous origin seen in metastatic pulmonary nodules, and the large malignant osteoblasts are not the type of cell seen in hemangiomas that undergo malignant change.

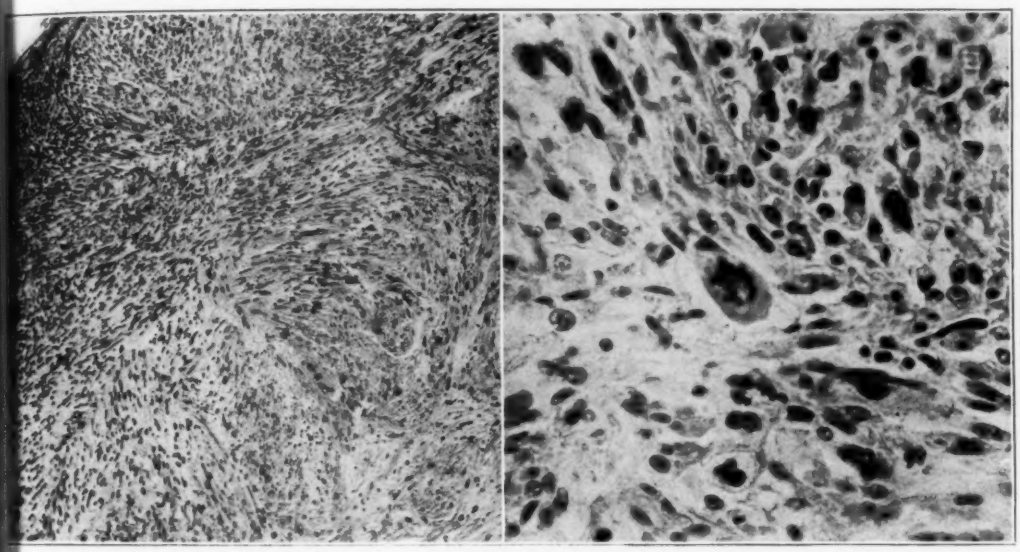

Fig. 65 (P. N. 38882).—Low and high power photomicrograph showing the hyperchromatism and pleomorphism associated with the osteolytic types of osteogenic sarcoma occurring in patients under 30 years of age. The low power photomicrograph emphasizes the connective tissue origin of the neoplasm; the high power, its tendency to differentiate into osteoblasts.

Histogenesis.—A study of the gross specimens and the roentgenograms in the cases of osteolytic sarcoma readily confirms the conclusion that this tumor at its time of origin and in its early phases is confined to the medullary spaces or cancellous structures within the area encircled by the cortical layers of the bone. Microscopic evidence supports the view that the neoplasm represents an early phase of osteogenesis via fibrous tissue. The spindle cells, although showing many signs of pleomorphism and malignancy, differentiate into osteoblasts of an abortive variety, and the tendency toward the production of bone is indi-

cated by the small amounts of osteoid tissue which can be found even in the metastatic pulmonary nodules. In tracing the histogenesis of this tumor, therefore, it is necessary to account for the central origin of the osteogenesis that is in progress and to seek an explanation for the failure of the process to achieve the formation of fully developed new bone and to result instead in a condition characterized by osteolysis.

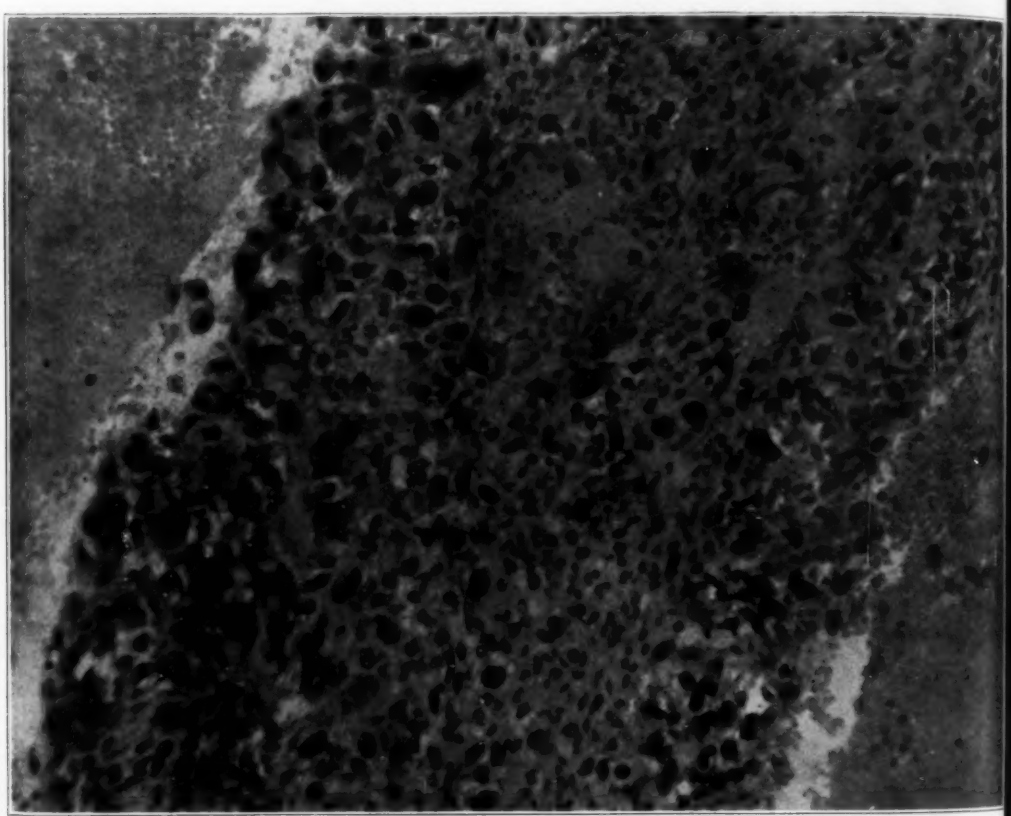

Fig. 66 (P. N. 41194).—Photomicrograph showing the malignant round cells referred to as abortive osteoblasts. Note the vascular spaces associated with the clinical features of aneurysm of the bone.

The answer is to be found in the type and localization of the connective tissue functioning in the regions in which this neoplasm takes its source. This tissue comprises the endosteum of the bone and is concerned in the formation of the cancellous portion of the bone structure that follows on the resorption of calcified cartilage.

In human embryos of from 120 to 140 mm., the sections of the long bones show an early cartilaginous stage of development in the

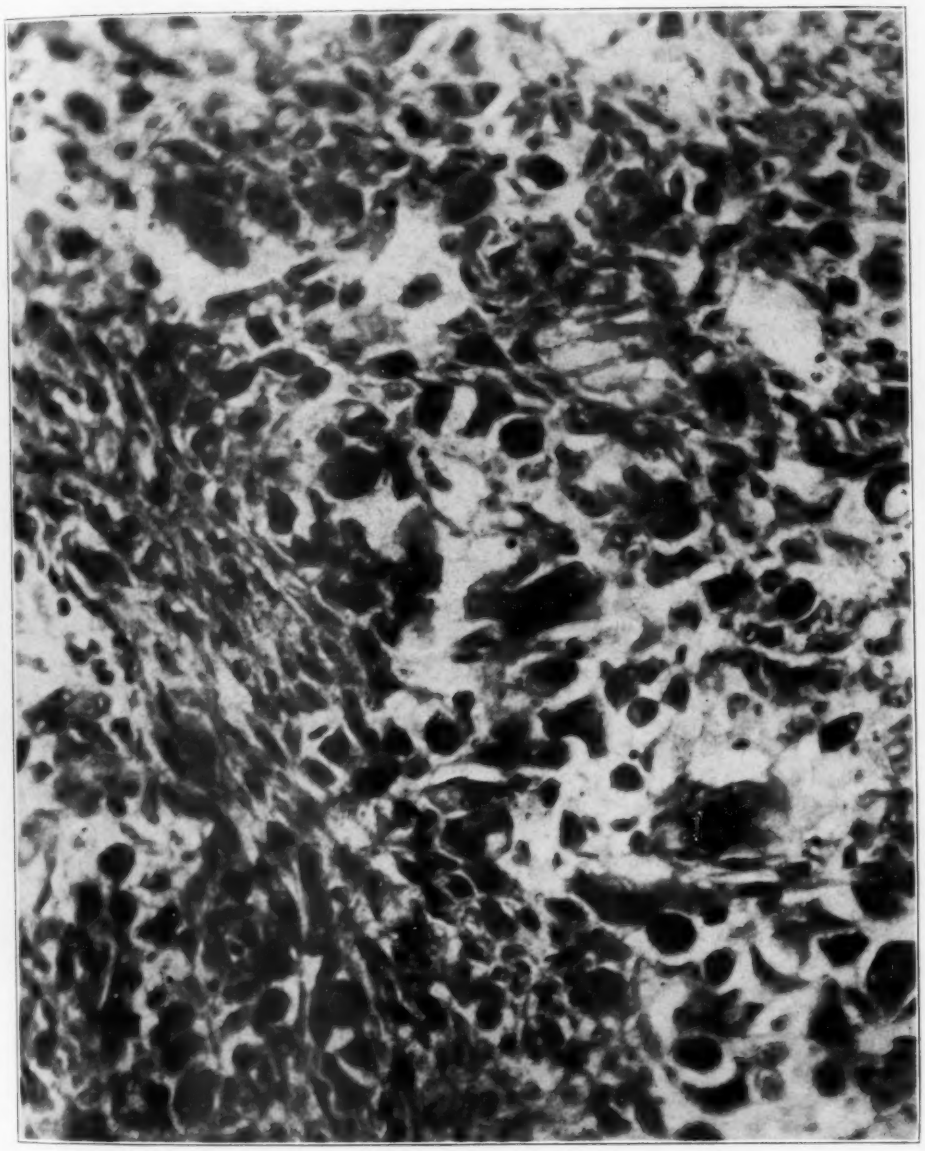

Fig. 67 (P. N. 36724).—Photomicrographs showing the tendency of small giant cells of the epulis type to be associated with malignant tumor giant cells in osteolytic sarcoma. The small giant cells of the epulis type are intermingled with spindle cells and early osteoblasts. The roentgenogram of this case is shown in figure 55.

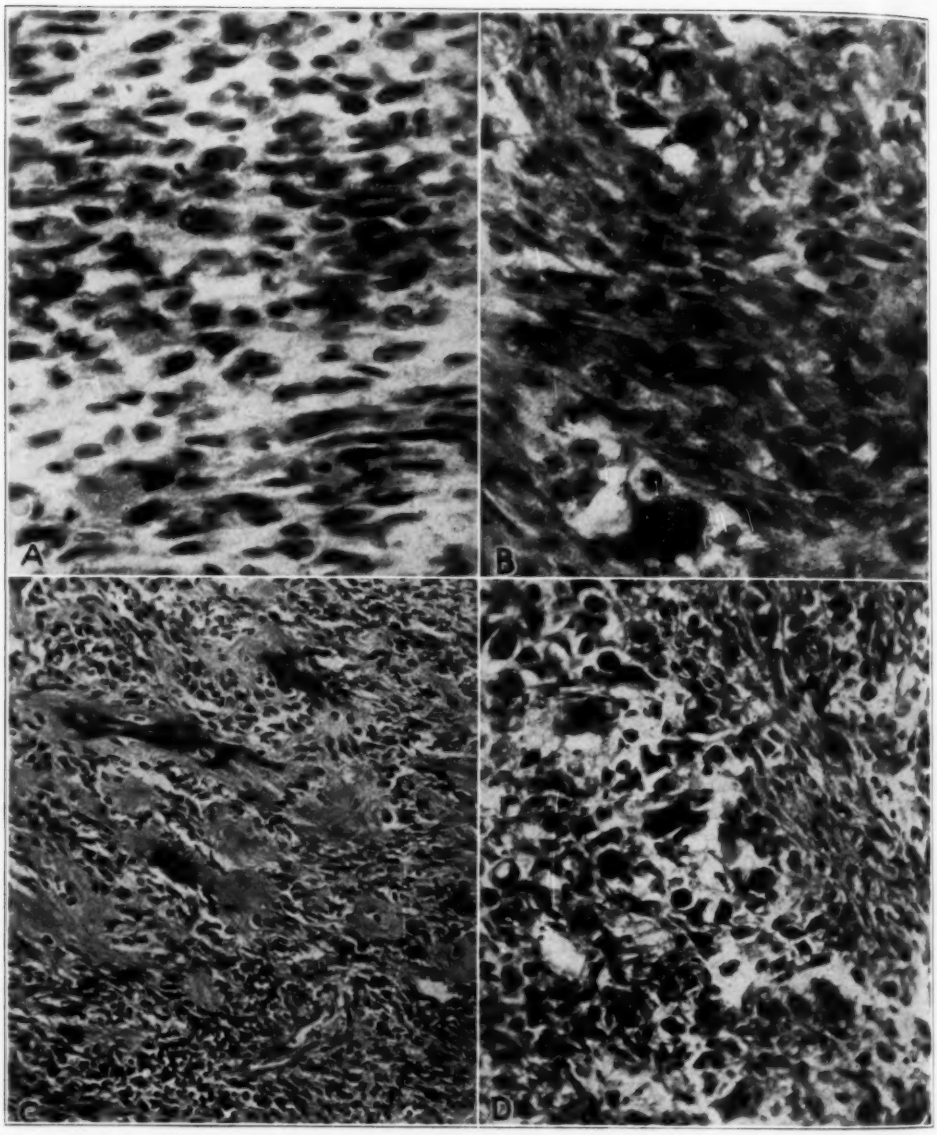

Fig. 68.—Photomicrographs showing the histogenetic cycle in osteolytic sarcoma. *A* shows malignant spindle cells predominating. The nuclei are large and vesicular. Mitotic figures are frequent. *B* shows a structure of malignant spindle and round cells. Abortive osteoblasts predominate. *C* depicts small osteoblasts associated with imperfect bone formation. This section was taken from a metastatic pulmonary nodule and shows more osteoid substance than is usually found in these new growths. *D* pictures a predominance of abortive osteoblasts intermingled with an imperfect osteoid substance which is being resorbed by small giant cells.

skeleton in the regions of the epiphysis and the metaphysis, but throughout the diaphysis of the bone ossification is in progress. At this stage the cortex is being re-formed, perforated by channels of the future haversian system, and the cartilage at the core of the bone is being resorbed to create a vascular cavity. Where a rim of cortical bone can be seen in cross-section, a layer of osteogenic tissue is visible on both sides—the outer layer constituting the periosteum and the inner

Fig. 69.—Cancellous bone formation in a human embryo of 150 mm. The mixture of hemorrhage, giant cells, spindle cells and osteoblasts among the bone spicules shows the same combination of cellular elements found in osteolytic sarcoma arising in cancellous bone.

layer the endosteum (fig. 69). At this stage ossification appears more active on the endosteal side, but the significant fact is that newly formed vessels are prominent, and spindle cells and round cells of the osteoblastic type are abundant, a picture not far removed from that seen in osteolytic sarcoma. The important point is that endosteal ossification following in the wake of calcified cartilage occurs in a tissue composed of a mixture of round and spindle cells and new blood vessels, pre-

senting an appearance similar to osteolytic sarcoma (fig. 70). This process, it is believed, is different from the direct membranous ossification that occurs after the periosteum has become more highly differentiated. It is more rapid, cellular and vascular. It is to be inferred, therefore, that the osteolytic sarcoma arises in ossification of this endosteal type, and its cellular and hemorrhagic character is a constant accompaniment of this primitive postcartilaginous formation of bone.

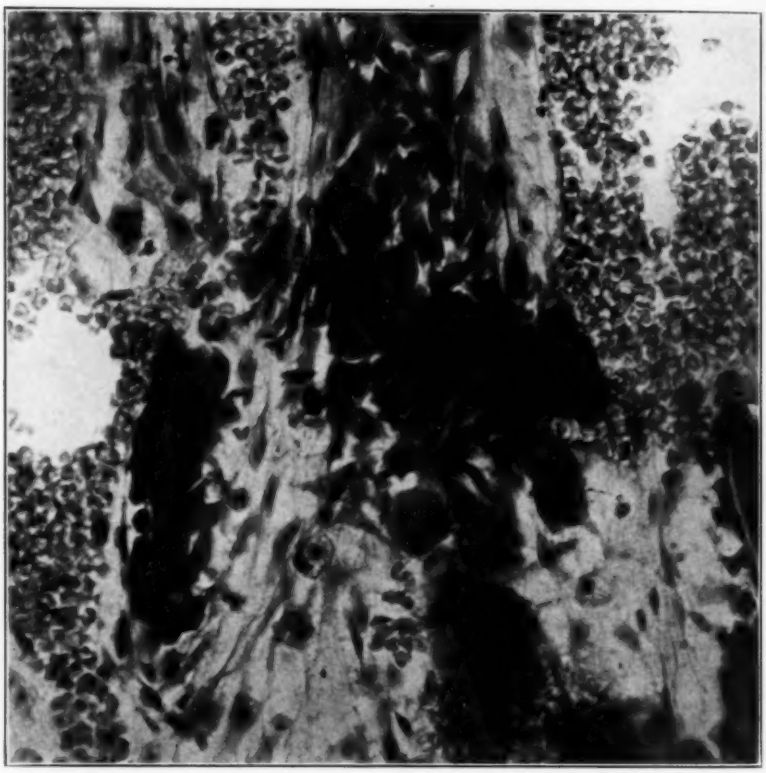

Fig. 70.—Higher magnification from the same embryo shown in figure 69. This picture emphasizes mixed spindle and round cells in an area of hemorrhage. The bone spicule in the center of the picture is being resorbed.

The failure of the osteolytic type of sarcoma to produce a state of adult bone is to be ascribed to the dependence of ossification in this type of tissue on the presence of calcified cartilage undergoing resorption. While in the embryo the entire core of the future bone provides such a warehouse of cartilage for the storage of calcium, after birth at the age periods when osteolytic sarcoma becomes clinically manifest no such adequate supply of calcified cartilage is available, and the pre-

osseous cellular tissue in the sarcoma readily outstrips the formation of osseous substance. The vessels accompanying this endosteal tissue proliferation may be a factor in eroding the structures of the bone, but in all probability the sarcomatous tissue itself enclosed within the cortical layers may be responsible for pressure atrophy, which in turn opens up numerous vascular channels in the medullary cavity.

The majority of cases of osteolytic sarcoma arise within cancellous bone in the metaphyseal region in patients under 20, which seems to indicate that the neoplasm has its source in a normal growth process concerned in the development of cancellous bone in its metaphyseal region during puberty. The normal growth impetus underlying this sarcoma, when it occurs in young patients, accounts in part for the poor prognosis in persons thus affected.

There is, however, another group of osteolytic sarcomas that are histologically of the same type and that occur in patients over 30, in whom the outlook is not so grave and in whom the duration of symptoms dates back not months but years. The question arises: Is there a secondary form of osteolytic sarcoma which follows on some benign chronic condition and which would thus explain this more protracted clinical picture? This question is intimately connected with the problem of so-called metastasizing giant cell tumor, and, as was brought out in a previous contribution,[3] in some of these cases of metastatic giant cell lesions the possibility that a secondary sarcoma arose at the site of an unhealed benign lesion must be seriously considered.

Unfortunately, there is no proved case in which microscopic tissue has been preserved when a benign persisting giant cell tumor later gave rise to this form of sarcoma, but the possibility cannot be denied. In some isolated cases the history would seem to indicate that localized areas of Paget's disease or an old fracture might have been the seat of such a secondary malignant growth. All of the patients in this series over 30 years of age have been examined carefully, and the data at hand leaves the matter still in doubt. While in about one third of the cases a residual osteomyelitis, an old fracture or severe trauma many years before or a lesion treated as a benign giant cell tumor is revealed in the history, there is microscopically and in the roentgenogram no evidence by which the benign condition can be definitely connected with the sarcoma that developed later.

The important phases of these supposedly secondary osteolytic sarcomas, regardless of the ultimate status of their etiology, concern the clinical course and ultimate result. As is brought out in the discussion of prognosis and treatment, patients with this secondary form of sarcoma are more apt to be permanently cured by radical operation and even when dying of metastasis may have a postoperative duration of life exceeding five years.

Prognosis and Treatment.—Of eighty-seven cases in the osteolytic sarcoma group, sixty-four were followed more than five years, and those in which the patient may be considered as permanently cured, i. e., living beyond five years, number only four, or about 6 per cent of the total. All of these patients were treated by amputation, usually following an exploratory operation after one or more weeks. In the cases terminating fatally, four of the patients were treated by irradiation either preoperatively or postoperatively without effect, nor did erysipelas and prodigiosus toxins (Coley's) in the five cases in which it was used affect the ultimate outcome. The striking feature in the cases in which cure was obtained is the age of the patient, which in three of the four cases was 30 years or over, and the duration of the symptoms, which was usually over eighteen months and averaged over four years. This is remarkable, because most of the patients with this form of sarcoma are between the ages of 10 and 20 years and give a history of symptoms of less than one year in duration.

In regard to the curability of this form of osteolytic sarcoma, therefore, one must conclude that only in the exceptional case in which the patient is an adult and the disease has run a protracted course and in which *amputation* preferably without irradiation is employed can favorable results be achieved. Even in such cases there is a possibility that while the patient will live over five years after operation he may ultimately succumb to metastasis. There are four such patients in this series, who lived from five to seven years after operation, but who finally died with pulmonary metastases. These four cases have not been included in the five year cures although possibly they are entitled to consideration as such, and if so considered would raise the percentage of cures in this group to 12 per cent. In each instance of these protracted cases the initial diagnosis was a benign giant cell tumor, and the original sections showed many giant cells. This mistaken diagnosis also was made in one of the cases placed among the bona fide five year cures.

In the younger patients, regardless of the form of therapy, the duration of life after treatment may usually be prophesied according to the duration of symptoms before examination. In this series the symptoms average eleven months and the postoperative duration of life an equal period, giving a total clinical course of something under two years.

The prognosis and results of treatment in the more chronic forms of osteolytic, osteogenic sarcoma occurring in adults are similar to the results of treatment analyzed in secondary chondrosarcoma, and support the inference that the more slowly growing and more readily curable instances of this disease are secondary to some preceding benign lesion.

THE SCLEROSING FORM OF OSTEOGENIC SARCOMA

The most highly differentiated periosteal sarcoma is the osteoblastic or sclerosing type. This osteoblastic or sclerosing form is the most emphatic bone-forming tumor in the group of osteogenic sarcoma, since it arises in the subperiosteal tissues capable of direct osseous formation. It is this particular tumor, characterized in the x-ray film by dense, shaggy new bone in the periosteal zone near the ends of the long bones in patients between the ages of 10 and 25 years, with which clinicians and roentgenologists are most familiar, and which is most commonly diagnosed correctly as sarcoma of the bone. Microscopically, large round cells or osteoblasts producing an abundant matrix of osteoid tissue are responsible for the new growth.

Clinical Features.—Although the sclerosing form of osteogenic sarcoma with its "sun-ray" appearance in the roentgenogram is the most universally recognized type, it is not the most frequent and ranks third, with 75 cases among a total of 360 osteogenic sarcomas forming the basis of this study. Among the clinical features of this group, the narrow age limits, the characteristic location and the brief duration of the symptomatology are outstanding. The majority of patients with sclerosing sarcoma of the bone are between the ages of 15 and 25 years. In the series under analysis, 41 cases occurred in this decade, 16 in the preceding decade (from 5 to 15 years) and 9 in the succeeding decade (from 25 to 35 years). There were only 5 cases in persons not in these three decades: a congenital tumor was discovered in the femur of a baby 16 days old (fig. 71) and the others were elderly adults (table 5). Most of the lesions were situated in either the lower end of the femur or the upper end of the tibia, nearly 80 per cent of the tumors being thus accounted for. The remainder occurred in the upper extremity, with a few isolated cases in the ribs and vertebrae, the pelvis and about the skeletal trunk. The most striking feature of the location of these tumors, however, is not the bone affected, but the region of the bone involved. The favorite site of origin of these growths is neither the shaft nor the epiphysis, but the metaphyseal side of the epiphyseal line. The significance of this distribution is strikingly emphasized by the study of the histogenesis of these tumors which is presented subsequently.

The duration of symptoms in this group of sarcomas of the bone averages under ten months. Trauma, pain, tumor and dysfunction are the usual sequence of events, trauma occurring at the onset of approximately one half the cases adequately recorded. Pathologic fracture is rare and was listed only five times in the present series. Examination of the affected extremity usually shows a visible and palpable swelling of bony hardness near the end of the bone. Cutaneous changes are not marked over tumors of moderate size, and the slight limitation of motion

TABLE 5.—*Osteogenic, Sclerosing Sarcoma*

P. N.	Race, Sex and Age			Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
42852	W	F	35	Femur, lower	16	Pain, tumor, limp	Sclerosing periosteal	Amputation, May, 1930	Ossification, osteoblasts, spindle cells, cartilage	.....
42180	W	F	17	Femur, lower	6	Pain, tumor, limp	Sclerosing periosteal	Amputation, Nov. 2, 1929	Ossification, osteoblasts	.....
40876	W	M	18	Tibia, upper right	2½	Tumor, pain	Sclerosing periosteal	Amputation, advised Sept. 12, 1928	.....	.....
40706	...	..	..	Tibia, upper	..	.....	Sclerosing periosteal	Amputation	.....	.....
40318	W	F	19	Femur, lower	..	.....	Sclerosing periosteal	Excision, Aug. 15, 1929	Ossification, osteoblasts, spindle cells, cartilage	.....
40026	W	F	9	Ilium, right	5	Pain, tumor	Sclerosing periosteal	Preoperative irradiation; colloidal lead, Jan. 18, 1928	.....	.....
39794	W	M	15	Femur, lower right	½	Tumor	Increased density, parallel periosteal reaction, expansion	Amputation, December, 1927	Ossification, osteoblasts, spindle cells	.....
39462	W	F	14	Tibia, upper	1½	Pain, tumor	.....	Cauterization, June 30, 1927; amputation, July 16, 1927	Ossification, osteoblasts, spindle cells	Dead 9 mos. after amputation
39382	W	F	16	Humerus, upper	6	Trauma, pain, tumor	Sclerosing periosteal	Amputation, July 2, 1927	.....	Dead after operation
39114	W	M	21	Femur, lower left	3½	Tumor, pain	Sclerosing periosteal	Amputation, April, 1927	Ossification, osteoblasts, spindle cells	Well almost 3 yrs. later
38566	W	M	..	Femur, shaft	2	.....	Sclerosing periosteal	Amputation	Ossification, osteoblasts, spindle cells	.....
38352	W	M	26	Femur, lower left	36	Trauma, pain, tumor	Sclerosing periosteal	Exploration, amputation, Sept. 13, 1926	Ossification, osteoblasts, spindle cells	Dead 18 mos. later
37938	W	M	7	Radius, lower	1	Tumor	Sclerosing periosteal	Excision, May 31, 1926 (complete, including end of radius)	Ossification, osteoblasts, spindle cells, cartilage	Dead 6 mos. later
37832	C	M	16	Tibia, upper shaft	..	Trauma	Sclerosing periosteal	Amputation, October, 1926	.....	Dead 4½ mos. later
37450	W	M	24	10th rib, right	6	Trauma, tumor, pathologic fracture	Sclerosing periosteal	Preoperative irradiation and resection advised, Dec. 30, 1925	.....	Dead 1 yr. later
37178	W	F	18	Femur, shaft, right	10	Trauma, pain, tumor	Sclerosing periosteal	Exploration and amputation, Nov. 30, 1925	Ossification, osteoblasts	Dead 5 mos. later
37018	W	M	15	Tibia, upper	4	Trauma, pain, tumor	Sclerosing periosteal	Irradiation advised, Sept. 1, 1925	.....	Dead 6 mos. later
36848	W	F	10	Humerus, lower shaft, right	2	Pain, tumor	Sclerosing periosteal	Exploration and amputation, July 10, 1925	Ossification, osteoblasts	Well 5 yrs.
36556	W	16 days		Femur, upper left	Congenital	Pathologic fracture, tumor	Sclerosing periosteal	X-ray, May 18, 1925	.....	Dead 3 mos. later
36112	W	F	13	Humerus, upper	..	.....	Sclerosing periosteal	Amputation, Nov. 6, 1924	Ossification, osteoblasts, spindle cells	Dead 21 mos. later
35786	W	M	15	Femur, upper right	4	Trauma, tumor, pain	.....	Amputation, Nov. 3, 1924	Ossification, osteoblasts, spindle cells	Dead 3 mos. later
35694	W	M	26	Femur, shaft, right	3	Pain, tumor	Sclerosing periosteal	Irradiation, July 30, 1924	.....	Dead 13 mos. later
35672	W	M	25	Femur, lower right	..	.....	Sclerosing periosteal	Amputation, Sept. 22, 1924	Ossification, osteoblasts, spindle cells	Local recurrence; dead 7 mos. later
34540	W	M	15	Femur, lower shaft	1½	Trauma, pain	.....	Cauterization, Sept. 8, 1923; amputation, Sept. 21, 1923	Ossification, soteoblasts, spindle cells	Dead 17 mos. later

34634	W	M	15	Femur, lower shaft	1½	Pain, tumor	Sclerosing periosteal	Amputation	.....	Dead after operation
34530	W	M	15	Femur, lower	2	Trauma	Sclerosing periosteal	Curettement, Sept. 8, 1923; amputation, Sept. 21, 1923	Ossification, osteoblasts, spindle cells	Dead 17 mos. later
34298	W	M	54	Vertebra, 2d and 3d lumbar	18	Tumor, pain	Sclerosing periosteal	Irradiation, 1920	Ossification, osteoblasts, spindle cells	Dead 18 mos. after appearance of symptoms
34104	W	M	22	Femur, lower	14	Trauma, pain, tenderness	.....	Amputation, Oct. 25, 1923	Ossification, osteoblasts, spindle cells	Dead 2 mos. later
33425	W	M	10	Scapula, right	4 da.	Trauma	.....	.....	.....	Dead 18 mos. after onset
33007	W	M	19	Fibula, upper	..	.....	.....	Excision, radium, amputation	Ossification, osteoblasts, spindle cells	Dead 5 mos. after excision
32749	W	F	14	Femur, lower right	8	Pain, tumor	Sclerosing periosteal	Irradiation, April 17, 1923	.....	Dead 15 mos. later
32132	W	M	18	Femur, lower	9	Pain, tumor	.....	Amputation, Jan. 25, 1923	Ossification, osteoblasts	Well 4 yrs., 10 mos. later
31935	W	M	15	Fibula, upper left	..	.....	Sclerosing periosteal	Amputation, Jan. 5, 1923	Ossification, osteoblasts, spindle cells	Well 5 yrs., 9 mos. later
31892	W	F	..	Femur, lower	..	.....	.....	Excision, Dec. 11, 1922; amputation, Dec. 18, 1922	Ossification, osteoblasts, spindle cells	Dead 11 mos. after amputation
31809	W	F	8	Humerus, upper left	9	Trauma, pain, swelling, pathologic fracture	Sclerosing periosteal	.....	.....	Dead
30650	C	M	6	Femur, lower	..	Trauma, tumor	Sclerosing periosteal, some destruction	Exploration, excision	.....	Dead after second operation
30616	W	M	20	Femur, upper right	24	Pain, tumor	Sclerosing periosteal	Exploration, June 17, 1922; amputation, Dec. 29, 1922	Ossification, osteoblasts	Dead 1 yr. after amputation
30548	W	F	38	Rib, fourth	12	Pain	.....	Irradiation, amputation, Dec. 1, 1921	Ossification, osteoblasts, spindle cells	Well 8 yrs. later
30188	W	M	13	Femur, lower	½	Trauma	Sclerosing periosteal	.....	.....	Dead in less than 1 yr. after appearance of symptoms
29663	W	M	25	Femur, shaft	48	Swelling	.....	.....	.....	Lost
29000	W	F	25	Femur, lower	11	Trauma, pain, tumor	.....	Amputation, Nov. 4, 1921	Ossification, osteoblasts, spindle cells, cartilage	Dead 6 yrs. later
28916	W	F	19	Tibia, upper	11	Trauma, pain, tumor	Sclerosing periosteal, some osseous destruction	Exploration, July 19, 1921; amputation, July 20, 1921	Ossification, osteoblasts, spindle cells	Well 6½ yrs. later
28352	W	M	67	Ulna, olecranon	15	Trauma, fracture pain, tumor	.....	Amputation, Dec. 10, 1919	Ossification, osteoblasts, spindle cells	Dead 2 yrs., 4 mos. later
28321	W	F	34	Femur, lower	72	Trauma (6 yrs.), pain, tumor, (1 yr.)	.....	Amputation, May, 1918	Ossification, osteoblasts, spindle cells	Dead nearly 7 yrs. later
28278	W	F	27	Radius, upper left	48	Fracture, 4 yrs.; tumor, 1½ yrs.	Sclerosing periosteal, osseous destruction	Amputation, Jan. 2, 1913	Ossification, osteoblasts, spindle cells	Well almost 12 yrs., lost
27753	W	F	30	Femur, lower	12	Pain, tumor	Sclerosing periosteal	Amputation, April 5, 1921	Ossification, osteoblasts, spindle cells	Dead 2 yrs., 9 mos. later
27578	W	F	6	Femur, lower left	..	Trauma, pain, tumor, pathologic fracture	Sclerosing periosteal, some destruction	Aspiration, Jan. 25, 1921; radium and irradiation; amputation, May 20, 1921	Ossification, osteoblasts, spindle cells	Well over 9 yrs.
27325	W	F	16	Skull, parietal left	2	Tumor	.....	Preoperative x-ray; partial excision, Dec. 30, 1920; postoperative irradiation, radium	Ossification, osteoblasts and early spindle cells	Dead 6½ mos. after operation

TABLE 5.—*Osteogenic, Sclerosing Sarcoma—Continued*

P. N.	Race	Sex	Age	Location	Duration, Mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Result
27282	W	M	15	Clavicle, midpart	3	Trauma, pain, tumor	Sclerosing periosteal, slight osseous destruction	Excision, Sept., 1920; preoperative x-ray	Ossification, osteoblasts, spindle cells	Well nearly 10 yrs. later
26917	W	F	18	Tibia, upper	3	Pain, swelling	Sclerosing periosteal	Curettement, August, 1920; radium, September, 1920	.....	Dead 2 yrs. after operation
26341	W	F	16	Rib, 11th right	36	Trauma, pain, tumor	.....	Excision, June 24, 1920 (of recurrence)	Ossification, osteoblasts, spindle cells	Dead 1½ mos. later
25761	W	M	18	Femur, upper	3	Trauma, pain, tumor	Sclerosing periosteal	Amputation, March 9, 1920	Ossification	Dead 3¾ mos. later
24856	W	F	20	Femur, lower left	..	Pain, tumor	.....	Amputation, Aug. 2, 1919	Ossification, osteoblasts, spindle cells, cartilage	Dead 4 yrs., 8 mos. later (other causes)
24428	W	M	18	Fibula, upper	2	Tumor	Sclerosing periosteal, slight destruction	Amputation, July, 1919; higher amputation, March 4, 1920	Ossification, osteoblasts, spindle cells	Dead 2½ yrs. after second amputation
24170	W	F	7	Femur, lower	2	Tumor, trauma, pain	Sclerosing periosteal	Exploration and amputation, Feb. 26,	Ossification, osteoblasts, early spindle cells	Well 6 yrs., lost
20547½	W	F	23	Femur, lower	3	Tumor	Sclerosing periosteal	Exploration, Jan. 27, 1917; excision, Jan. 27, 1917; radium and Coley's toxin; amputation, July, 1916	Ossification, osteoblasts, spindle cells	Dead 12 yrs. after amputation
17971	W	M	17	Femur, lower	5	Trauma, pain, tumor	Sclerosing periosteal	Amputation, Aug. 6, 1915	Ossification, osteoblasts, spindle cells	Dead 10 mos. later
17889	W	M	34	Thoracic wall	16	Pain (7 yrs.), tumor	.....	Coley's toxin; neoarsphenamine; partial excision, July 27, 1915	Ossification, osteoblasts, spindle cells	Dead 3 mos. after operation
16250	W	F	18	Tibia, upper	11	Pain, tumor	Sclerosing periosteal	Exploration and amputation, Sept. 24 1914	Ossification, osteoblasts, spindle cells	Dead 2 yrs. after operation
15480	W	M	17	Tibia, upper left	9	Trauma, pain, tumor	.....	Amputation, March 17, 1914	Ossification, osteoblasts, spindle cells	Lost
15213½	W	M	..	Femur, lower	..	Tumor, fracture	.....	Amputation, Jan. 18, 1913	Ossification, osteoblasts, early spindle cells	Well over 17 yrs. later
14817 (15838)	W	M	21	Humerus, upper	5	Swelling, pain, limitation of motion	Early sclerosing periosteal, marked osseous destruction	Excision and resection of upper end of humerus, Oct., 28, 1913; amputation, June 3, 1914	Ossification, osteoblasts, a few spindle cells	Dead 3 mos. after amputation
14426	W	M	21	Tibia, upper	12	Trauma, pain, tumor	.....	Amputation, July 16, 1913	Ossification, osteoblasts, spindle cells	Dead
14392	W	F	24	Femur, lower right	18	Trauma, pain, tumor	.....	Amputation, Aug. 8, 1913	Ossification, osteoblasts, spindle cells	Well over 16 yrs. later
14143	W	F	11	Tibia, upper	1½	Tumor	Sclerosing periosteal	Amputation, May 1913	Ossification, osteoblasts, spindle cells	Well over 14 yrs., lost
13142	W	M	22	Tibia, upper	5½	Tumor	.....	Amputation, Aug. 20, 1912	Ossification, osteoblasts, spindle cells	Dead 7 yrs. later
12221	C	M	52	Humerus, lower right	..	Pain	.....	Excision, Oct. 25, 1911	Ossification, osteoblasts, spindle cells	Lost
11254	W	M	19	Femur, lower	2	Pain, tumor	.....	Exploration, curettement, Feb. 13, 1911	Ossification, osteoblasts, spindle cells	Lost
9114	W	M	20	Tibia, upper	20	Pathologic fracture	Sclerosing periosteal, some osseous destruction	Excision, Feb. 28, 1907; excision, Oct. 8, 1907; excision, with part of bone, July 8, 1908	Ossification, osteoblasts, spindle cells	Dead 1 yr., 7 mos., after last operation
5701	C	F	26	Femur, lower	6	Pathologic fracture, tumor	Early sclerosing	Amputation, Aug. 26, 1906	Ossification, osteoblasts, early spindle cells	Lost
4323	W	F	14	Fibula, upper	36	Pain, trauma	Sclerosing	Amputation, June 23, 1902	.....	Well 5 mos., lost
1459	W	M	34	Femur, lower	36	Trauma, pain, tumor	.....	Exploration, amputation, Aug. 18, 1896	Ossification, osteoblasts, spindle cells	Dead 2 yrs., 4 mos. later
1264	W	F	13	Femur, lower	2	Pain, tumor	.....	Exploration, amputation, March 17, 1896	Ossification, osteoblasts, spindle cells	Dead

in the adjacent joint is of no clinical significance. Occasionally crepitis may be elicited by pressure on the bony spicules of the growth, but such manipulations are not to be encouraged when x-ray studies are available.

In one fifth of the cases leukocytosis or fever or both were recorded, which is about the usual incidence of these systemic reactions in rapidly

Fig. 71 (P. N. 36566).—Roentgenogram of a sclerosing osteogenic sarcoma occurring at birth in the metaphysis of the upper end of the femur. The baby was 16 days old when the film was made. There is marked periosteal new bone and secondary osseous destruction.

growing malignant neoplasms of the bone whether the patients are seen in either the earlier or later stages of the disease. No particular diagnostic importance should be attached to such findings unless the temperature equals or exceeds 102 F. and the leukocytes 20,000; above these limits, infection is to be suspected.

Roentgenographic Features.—The x-ray film furnishes the most helpful diagnostic data available to the practitioner in this group of cases. The usual roentgenogram of a bone affected with this form of osteogenic sarcoma shows an area on the shaft side of the epiphyseal line of a long bone (generally the lower end of the femur or the upper end of the tibia) in which dense formation of new bone is obliterating the normal osseous markings. In the marrow cavity, this sclerosis is

Fig. 72 (P. N. 29000).—A roentgenogram of sclerosing sarcoma showing marked sclerosis in the marrow cavity and periosteal zones. The patient had had symptoms of over eleven months' duration and lived over five years after amputation.

accompanied by some secondary destruction of the bone which may produce a slight mottling effect. In the cortical zone, the normal transition between marrow and cortex is usually obscured in the affected area by the osseous formation which extends into both medullary and periosteal zones. The periosteum above and below the main area of the tumor is raised, and where it resumes its contact with the bone, a triangle of

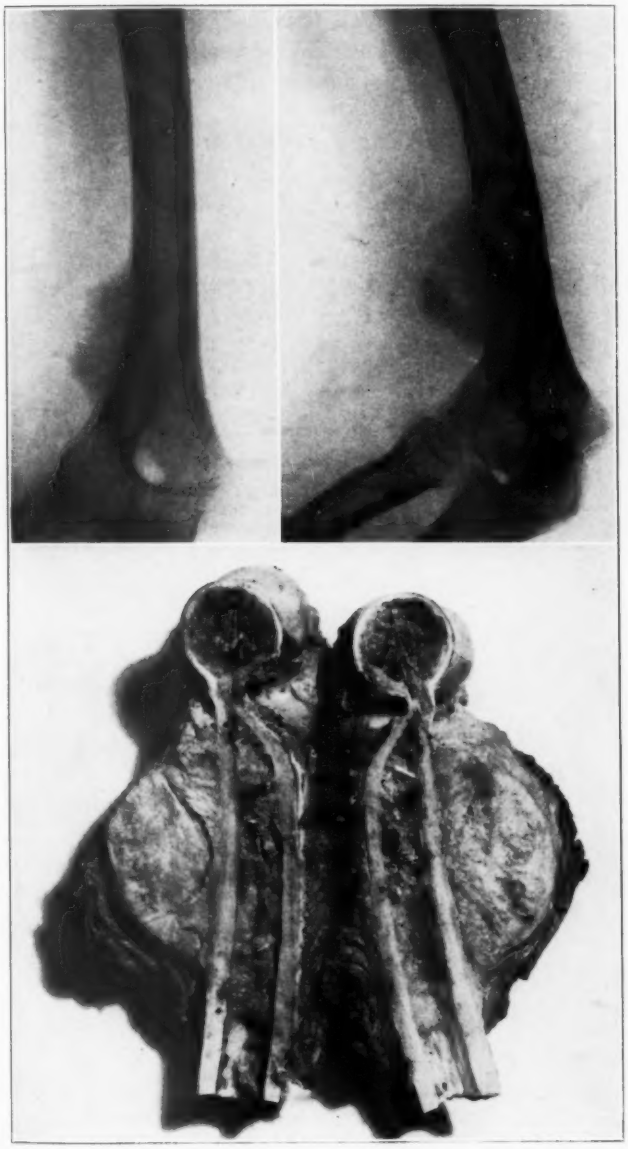

Fig. 73 (P. N. 36848).—An early case of sclerosing sarcoma occurring in a child of 10. The roentgenograms show new bone localized in the subperiosteal region of the metaphysis. In the gross specimen the cortex of the marrow cavity has not been invaded by the tumor. The lesion had been present two months before treatment, and the patient is living over five years after a resection of the lower end of the humerus.

ossification appears, known as periosteal lipping. Although this so-called lipping has been much stressed as a diagnostic feature of sarcoma, it is not rare in forms of periostitis unrelated to neoplastic disease.

The most striking affects are in the region of maximal periosteal separation, where radiating spicules of new bone, proceeding outward

Fig. 74 (P. N. 39114).—An early case of sclerosing sarcoma in which subperiosteal formation of new bone in the metaphyseal region predominates. The roentgenogram differs from chondrosarcoma in that slight sclerosis of the marrow cavity is present. The gross specimen shows clearly the fresh white osteoid substance and the slightly increased density in the cancellous bone beneath the cortex. This patient had symptoms of three and one-half months' duration, and is living approximately one year after amputation.

at right angles, are crowded together to give the characteristic shaggy, sun-ray appearance (fig. 72).

In studying a large series of x-ray films of cases in which the diagnosis was verified by pathologic examination, the roentgenograms may be grouped according to the duration of symptoms and the early and late phases of the growth compared. In the early cases of from two to four month's duration (figs. 73 and 74), the tumor is largely confined to a subperiosteal location, in which delicate radiating lines of new bone are visible beneath an area of raised periosteum, the cortex and marrow cavity being practically undisturbed. In the advanced cases

Fig. 75 (P. N. 30616).—A late case of sclerosing sarcoma occurring in a patient, aged 20, who had symptoms of two years' duration and who died twelve months later after an amputation at the hip joint. The roentgenogram shows marked sclerosis of the marrow cavity and the gross specimen, secondary destruction of the bone with pathologic fracture.

of from six to twelve months' duration (figs. 72 and 75), on the other hand, the periosteal new bone is not only more dense but the cortex and marrow cavity beneath are invaded and sclerosed and the growth extends lengthwise along the shaft. Areas of secondary destruction of the bone and pathologic fracture may eventually occur. It is clear from an analysis of the roentgenograms that the site of the origin of the tumor

is in the metaphyseal region in the subperiosteal zone of the long bones, where osteogenesis is proceeding most rapidly at the age period when these tumors occur.

Gross Specimens.—The gross specimens secured at operation by amputation provide one of the most valuable means of studying the origin and growth of this type of sarcoma of the bone. In all of the specimens available for study, twenty-two in all, the tumor proper was situated in the metaphysis, and the epiphysis was never primarily involved. In young patients with an unossified epiphyseal line, the epiphyseal cartilage walls off the tumor in that direction, and even in the advanced stages the epiphysis remains free while the growth extends

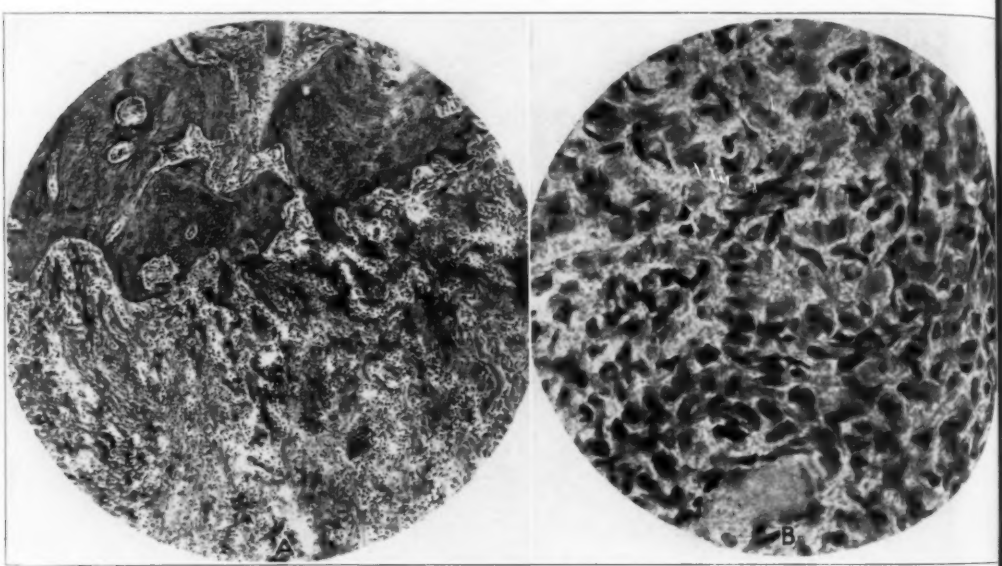

Fig. 76 (P. N. 30616).—Low and high power photomicrographs showing the large osteoblasts applied to the osteoid intercellular substance, typical of sclerosing sarcoma. (Same case as shown in figure 75.)

instead outwardly into the soft parts and upward along the shaft of the bone (fig. 77). In older patients, when the epiphysis has united, secondary involvement of the end of the bone occurs when the tumor has progressed without early operative intervention.

In early cases the bulk of the sarcomatous growth is found between the periosteum and the cortex of the bone on the shaft side of the epiphyseal line. The tumor tissue is firm in consistency, varying in density from that of solid fibrous tissue to the hardness of compact bone. Its structure shows a definite grain or fiber which runs outward from the shaft, more or less at right angles to its long axis (fig. 78).

The color is white, light gray or whitish pink. Hemorrhage, either old or recent, and cyst formation are practically always absent, unless the tumor has previously been explored. The ossifying neoplastic tissue is decidedly gritty to the touch and cuts poorly, or not at all when the knife is applied. At its extreme margin the raised periosteum bounding the tumor may be perforated, and the muscle invaded by white solid tumor tissue. This outer zone shows the most fibrillated structure with individual spicules of bone arranged in a radiating manner. As the cortex is approached, the tumor is more solid and assumes the structure of compact bone, its cut surface in these areas often appearing as frozen or like caked snow (fig. 74).

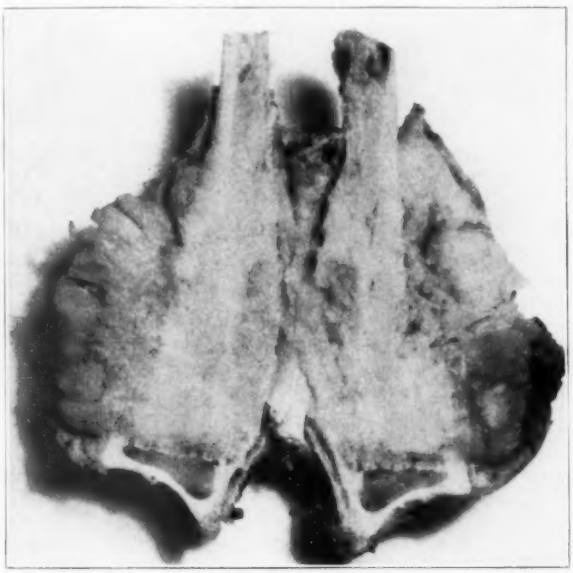

Fig. 77 (P. N. 37938).—A gross specimen of sclerosing sarcoma in a boy, aged 7. The pronounced formation of new bone which infiltrates into the marrow cavity and soft parts is effectively walled off by the cartilage of the unossified epiphyseal line.

Invasion of the medullary cavity is apparently secondary to the subperiosteal growth. The earliest change seen in the medullary cavity is the production of normal bone which reacts vigorously to early invasion of the tumor. This sclerosis of the medullary cavity, which is due to a combination of both the tumor bone and reactive bone, is generally less in amount than the subperiosteal tumor growth, but in rare instances may keep pace with it. As the tumor progresses, the neoplastic tissue gives rise to more and more compact bone, which although at first largely confined to the zone beneath the periosteum in a metaphyseal

location later extends throughout the entire area of the tumor, in the medullary cavity, in the subperiosteal regions and even in the soft parts. It is this picture of diffuse osseous consolidation seen in advanced cases that caused the older pathologists to apply the name of sclerosing sarcoma to this new growth.

Microscopic Features.—The microscopic studies confirm the view that the neoplastic process in this sarcoma involves tissue concerned in

Fig. 78 (P. N. 24856).—Gross specimen of a cured case of sclerosing sarcoma in a white girl, aged 20. This specimen shows the radiating fibers of the tumor mass proceeding outward from the cortex beneath the periosteum in the metaphyseal region of the bone.

direct osseous formation. The histology of all these lesions is essentially a proliferation of connective tissue passing through the stages of spindle cells, osteoblasts, osteoid tissue and new bone. Most of the sections are predominated by a proliferation of many osteoblasts with large deep staining vesicular nuclei and a cytoplasm pointed in one direction like the tail of a tadpole (fig. 79). Among these cells, a deep staining osteoid substance is found. This direct mode of ossification differs in

these sarcomas from benign reactive bone seen in inflammatory conditions and osteitis fibrosa in two outstanding respects. First, the osteoblasts predominate and great numbers are packed in among the

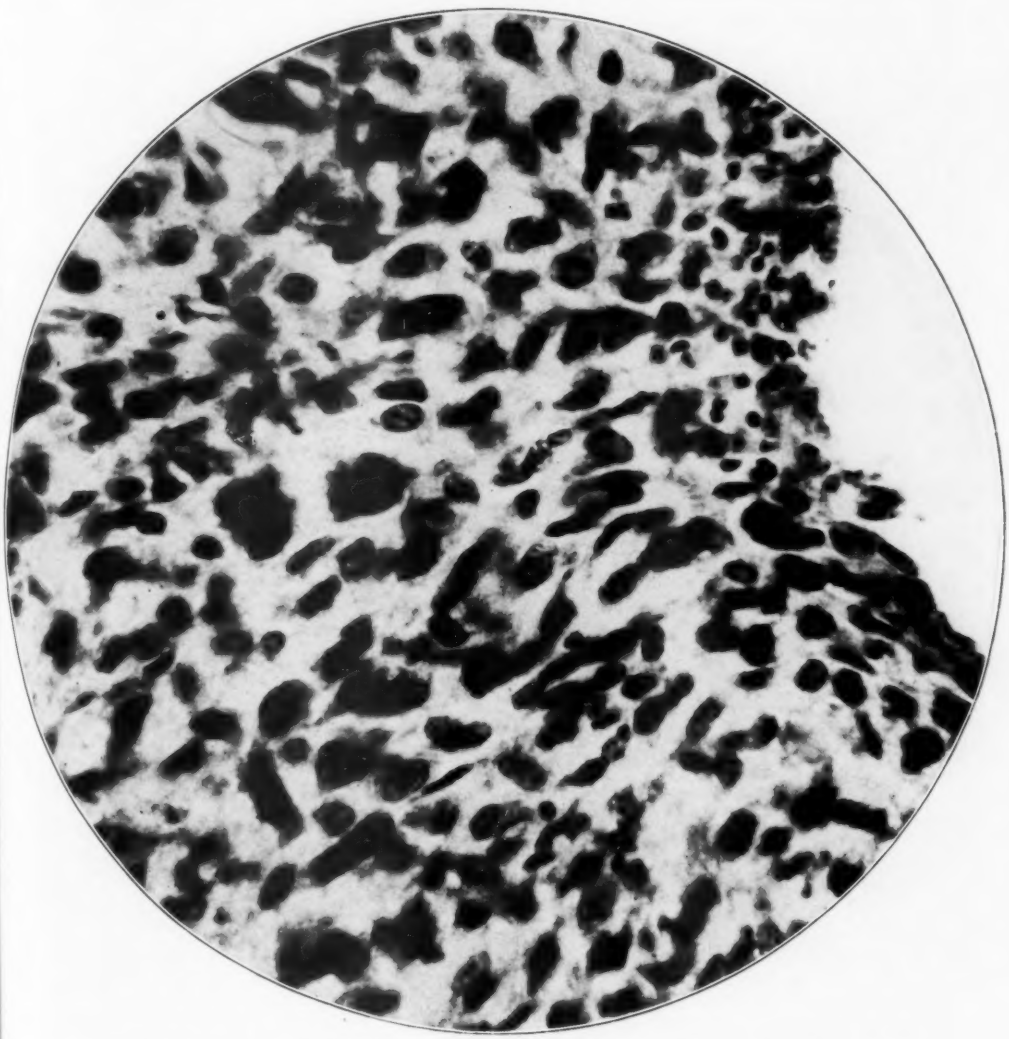

Fig. 79 (P. N. 14817).—Proliferation of numerous malignant osteoblasts in a case of sclerosing sarcoma. The osteoblasts have no definite relation to either bone spicules or osteoid substance.

osteoid tissue in a disorderly fashion. Unlike benign osseous formation of the membranous type, the osteoblasts vary in size, giving rise to numerous large binucleated forms, and they are not lined in orderly

rows about definitely formed bone spicules (compare figs. 79 and 80). Second, the osteoid tissue is laid down helter-skelter and bears no constant relationship to the amount of fibrous tissue or osteoblasts present. In some sections this osteoid substance may infiltrate everywhere, compressing the masses of osteoblasts between it. In other sections the

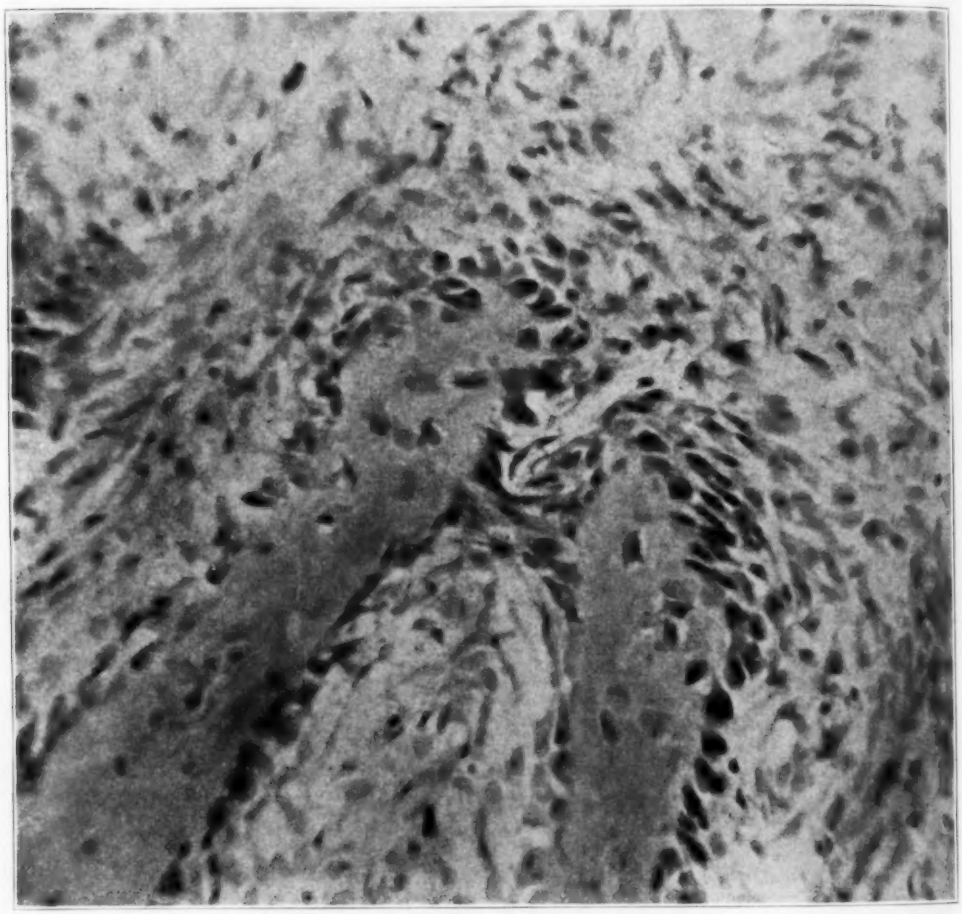

Fig. 80 (P. N. 14179).—The osteoblasts in new bone of the normal reactive type. The osteoblasts are relatively small, are associated with a preceding connective tissue containing many spindle cells and fibroblasts and are arranged in orderly rows about definite spicules of new bone. (Figures 79 and 80 demonstrate a comparison of the type of osteoblasts seen in malignant and normal bone formation.)

osteoid tissue may be relatively sparse, and the obsteoblasts and their precursors the fibroblasts may predominate, the osteoid substance being present only in scattered areas (fig. 81).

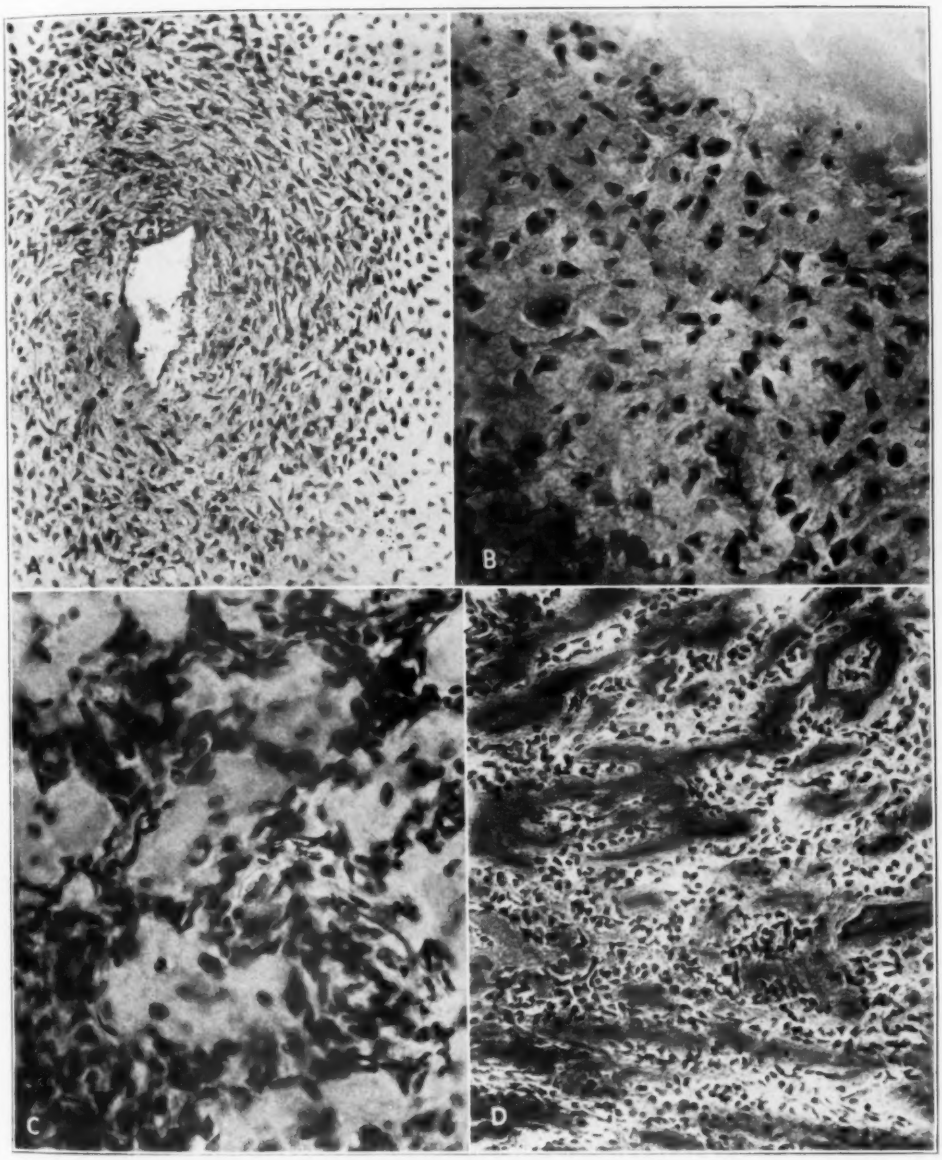

Fig. 81.—The histogenetic cycle of sclerosing osteogenic sarcoma. *A* shows the pre-osseous edema among malignant spindle cells and early osteoblasts, surrounding a small blood vessel. *B* shows definite osteoid material surrounding the cells which are predominantly osteoblasts. *C* shows the osteoid substance in early and indefinite spicule arrangement surrounded by malignant osteoblasts and spindle cells. *D* shows the formation of definite but irregular osteoid spicules, surrounded by a profusion of malignant osteoblasts.

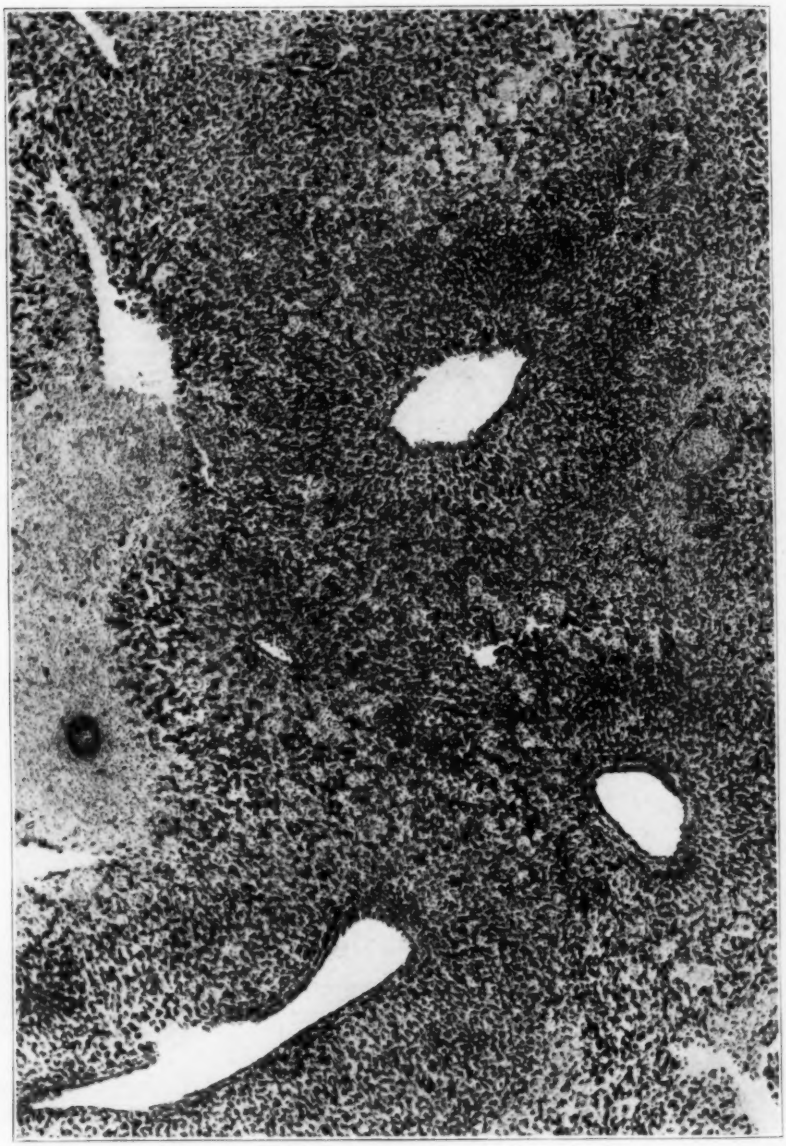

Fig. 82 (P. N. 14817).—Photomicrograph of an area in the same case shown in figure 79. The osteoblasts and spindle cells are grouped about blood vessels to give a characteristic perithelial arrangement.

While in the usual sclerosing osteogenic sarcoma, the microscopic features emphasize a highly differentiated type of osteogenesis characterized by direct formation of bone with a predominance of osteoid and osseous substance among a proliferation of osteoblasts; some of these tumors, despite their periosteal location, may show a slightly earlier

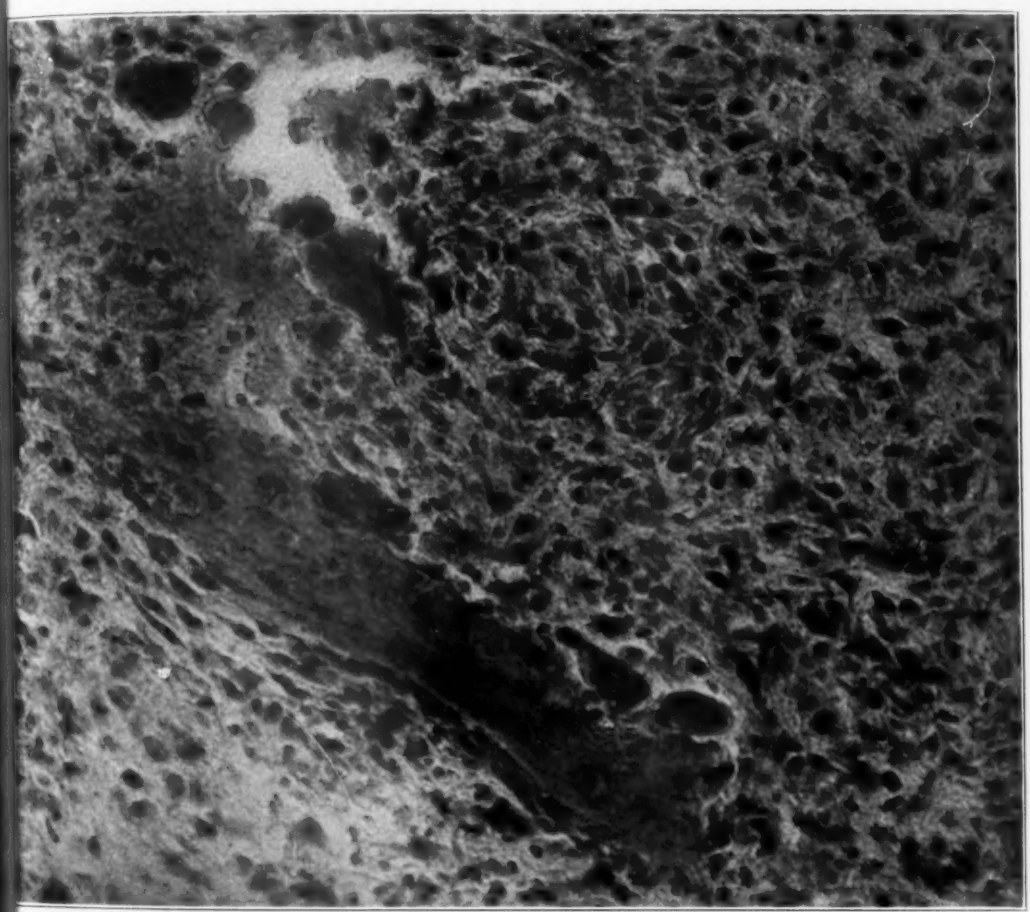

Fig. 83 (P. N. 27578).—Photomicrograph of a section taken from the margin of a sclerosing osteogenic sarcoma showing spicules of normal reactive bone being laid down beside an area of malignant osteoblasts intermingled with early osteoid substance. At the middle of the picture normal bone formation proceeding from the left is meeting malignant bone formation from the right. The result is the destruction of the normal bone spicules and their resorption by giant cell osteoclasts.

histogenetic phase. This early phase of the sclerosing form of osteogenic sarcoma is microscopically identical with the osteolytic form previously described. These tumors are rare and will be discussed subsequently

when variants of sclerosing sarcoma are considered. In fully developed cases, however, vascular tissue containing large malignant spindle cells, abortive osteoblasts and giant cells of the epulis type, such as are seen in sections of osteolytic sarcoma, are absent, although occasionally a blood vessel is seen, about which the malignant new bone may dispose itself in a more or less perithelial arrangement (fig. 82). Cartilage may occasionally be found in these new growths, but is never abundant,

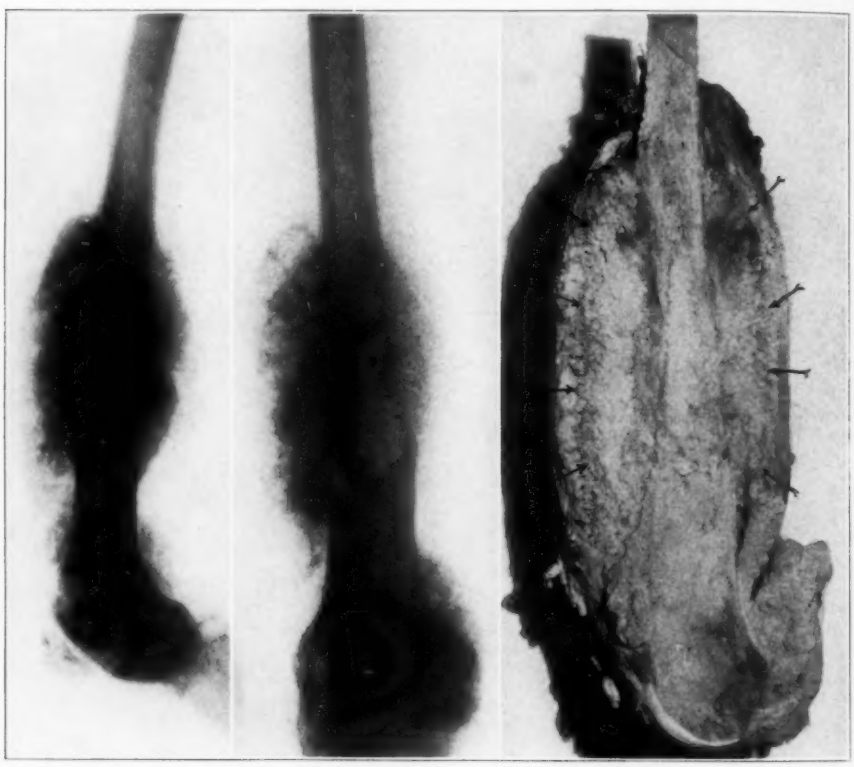

Fig. 84 (P. N. 43060).—Roentgenogram and gross specimen of a case of sclerosing sarcoma occurring in a white man, aged 49. This patient was fed a madder diet on four consecutive days preceding amputation. The result is depicted in the gross specimen. The growth of the tumor at its periphery is shown by the dark areas, the recent osteoid substance having taken up the red dye and staining this portion only. The dye unfortunately had faded somewhat when the photograph was made, and is indicated by the arrows. The other dark spots are hemorrhage.

and its appearance in the sections is sufficiently atypical to justify the consideration of these cases as variants. These chondral variants of sclerosing sarcoma involve an earlier type of periosteum which still retains remnants of its perichondrial origin.

Histogenesis.—The evidence accumulated in this study leaves little doubt as to the source of this form of osteogenic sarcoma. The tumor takes its origin in the osteogenic layers of the periosteum which are particularly active in the formation of compact bone in the metaphyseal region of young adults and children in the pre-adolescent period. All the roentgenograms and the gross specimens emphasize the metaphyseal location and the subperiosteal origin of these tumors. The fact that this subperiosteal region is not active about the epiphysis after the age of 3 explains why these ends of the bone are never primarily involved by this neoplasm. The midshaft regions are rarely, if ever, involved in

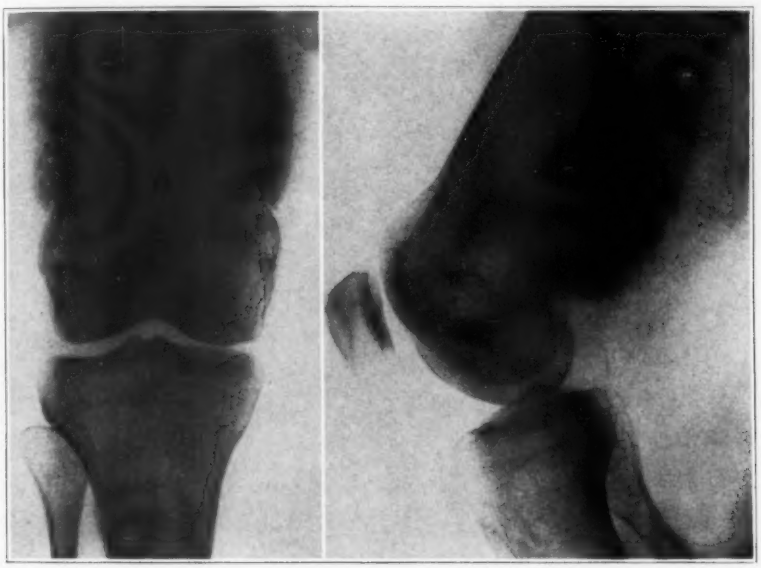

Fig. 85 (P. N. 42852).—A chondral variant of sclerosing osteogenic sarcoma, showing the typical sclerosing roentgenographic picture. (Operation by Dr. Dean Lewis.)

young adults, because this same subperiosteal tissue has ceased to function as an active center of growth in this region of the bone after birth.

Evidently, therefore, a normal histogenetic transition from early connective tissue through osteoblasts to osseous formation, occurring at a rapid rate during the period of normal adolescent growth is necessary for the development of this type of osteoblastic, osteogenic sarcoma. This is borne out by the microscopic studies of this neoplasm, because the histology manifested repeats in all of its essentials the normal mode of the formation of membranous bone characterized by connective tissue, osteoblasts and osteoid spicules typical of these subperiosteal osteogenic

layers. It is also confirmed clinically by the restricted age period in which these growths occur and their sharply delimited localization in the skeleton.

The mechanism whereby this normal type of growth and histogenesis are transformed into the disorderly and malignant histologic cycle typical of this form of sarcoma is obscure. Although trauma is recorded in

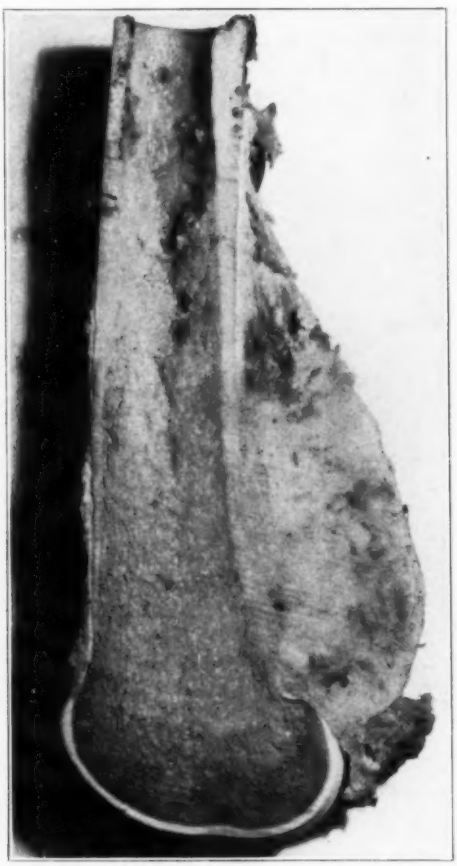

Fig. 86 (P. N. 42852).—The gross specimen of the case shown in figure 85. The bulk of the tumor mass is lying beneath the periosteum; the marrow cavity has not been invaded.

50 per cent of these lesions, no direct connection can be traced between the immediate result of the injury and the subsequent malignant response. The problem is rendered even more difficult because the defensive reaction on the part of the body is unquestionably performed by means of a proliferation of the same type of membranous bone as occurs in the formation of the malignant process, and this normal

development occurs simultaneously with the malignant and abortive form of the same process (fig. 83).

The feeding of madder (a vegetable dye originally used by John Hunter to study the growth of bone) to patients with this form of sarcoma, has been carried out previous to operation, and the subsequently amputated specimens have been examined. The dye localized in the areas of new bone but stained the osteoid substance rather than the cells concerned in osteogenesis. It was therefore possible to confirm the fact that the tumor was arising subperiosteally, and its most actively

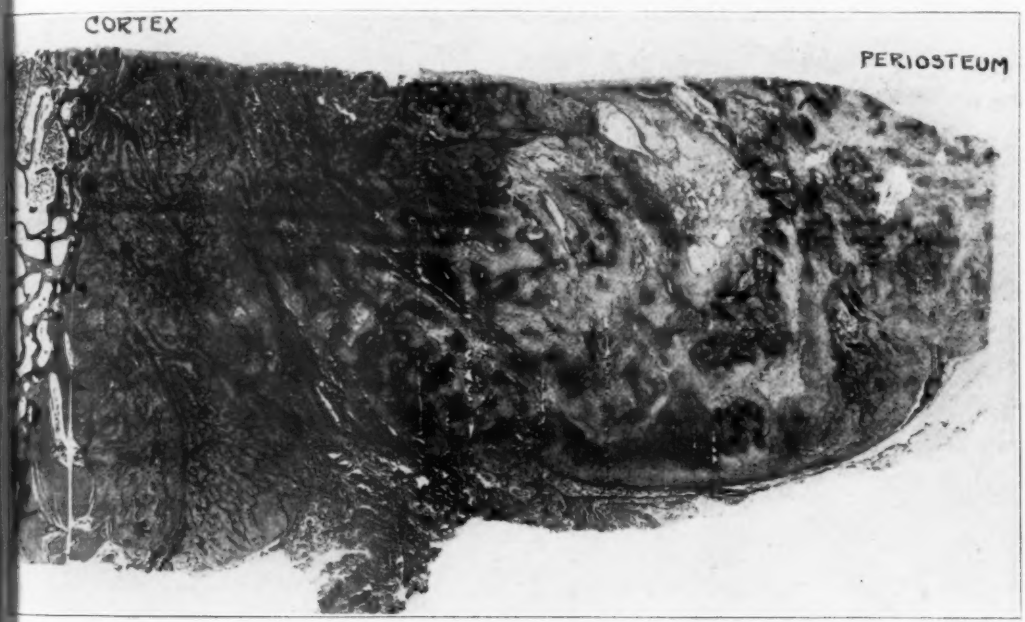

Fig. 87 (P. N. 42852).—Low power photomicrograph showing the lobular tumor mass ossifying beyond the cortex in the subperiosteal zone. (Same case as shown in figure 86.)

growing border was on the side of the periosteum rather than next to cortical bone, but the differentiation of the early malignant cells from embryonic cells of normal type concerned in the production of reactive bone was not accomplished (fig. 84).

Prognosis and Treatment.—Although the duration of the symptomatology is brief, averaging less than ten months, and the postoperative duration of life in fatal cases averages only fourteen months, the percentage of cures effected by radical operation is unusually great in this type of sarcoma. In sixty cases in which complete data were available, including follow-up study, extending over a period of five years

or more, there were sixteen cured patients living five years or longer. All these cures were effected by radical operation, amputation being performed when possible and radical resection in cases affecting the clavicle or rib. In all but two cases, the radical operation was instituted at once. In two of the living patients, however, there had been previous aspiration or exploration followed by amputation at an interval of weeks or months.

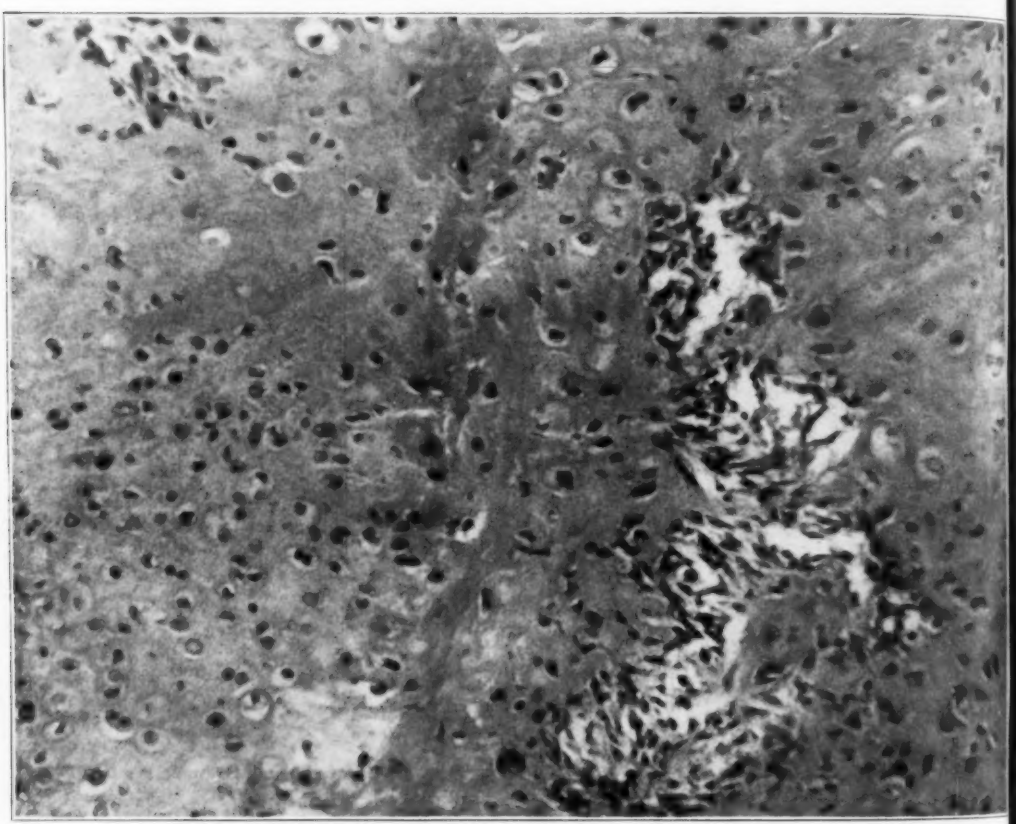

Fig. 88 (P. N. 42852).—High power photomicrograph showing a cartilaginous area undergoing conversion into an osteoid substance. (Same case as in figures 85 and 86.)

These data leave no question as to the procedure of choice in this type of sclerosing sarcoma of the bone. Radical amputation or resection should be performed at the earliest possible date, and if exploration is done this should be under the tourniquet. Frozen sections should be made with an immediate and competent pathologic report, and the operation proceeded with at once. If facilities for frozen section are

not available and consultation is required in the diagnosis, the roentgenograms and not the sections should be sent, as a diagnosis can usually be obtained roentgenologically without the necessity of exploration, if the proper authorities are consulted. This is the method advocated by Bloodgood.

Deep roentgen therapy does not result in cure in these cases and only restricts the rate of advance of the peripheral margin of the lesion. Two of the patients considered cured had received Coley's toxins in

Fig. 89 (P. N. 37008).—A mixed round and spindle cell variant of sclerosing osteogenic sarcoma. *A* shows the roentgenogram before exploration. The tumor mass is seen arising subperiosteally, causing periosteal lipping and producing a cloudy extracortical shadow rather than the characteristic picture of sclerosis. *B* shows the roentgenogram taken three months after that of *A*. There had been four local operations and the tumor is now frankly sclerosing in appearance.

addition to radical operation. Three had also had the benefit of postoperative irradiation.

In regard to the prognosis, it is possible to state that in the patient with the sclerosing sarcoma of the bone, regardless of age, provided the lesion is situated where complete resection or amputation is possible, the chances of cure are more than 25 per cent, if primary radical

operation is performed. This probability of a cure becomes less the longer the duration of symptoms prior to operation and the greater the interval of time elapsing between an incomplete primary operation and radical treatment. It can also be stated that patients surviving radical operation after eighteen months, who show no signs of recurrence or metastases at that time, will, in all probability, remain free from disease.

This high percentage of five year cures in osteogenic sarcoma is unusual, and the better prognosis in patients with this sclerosing form depends on the state of differentiation of the malignant cells or osteoblasts which represents the apex of development in the derivation of bone from connective tissue. The better prognosis in these sarcomas

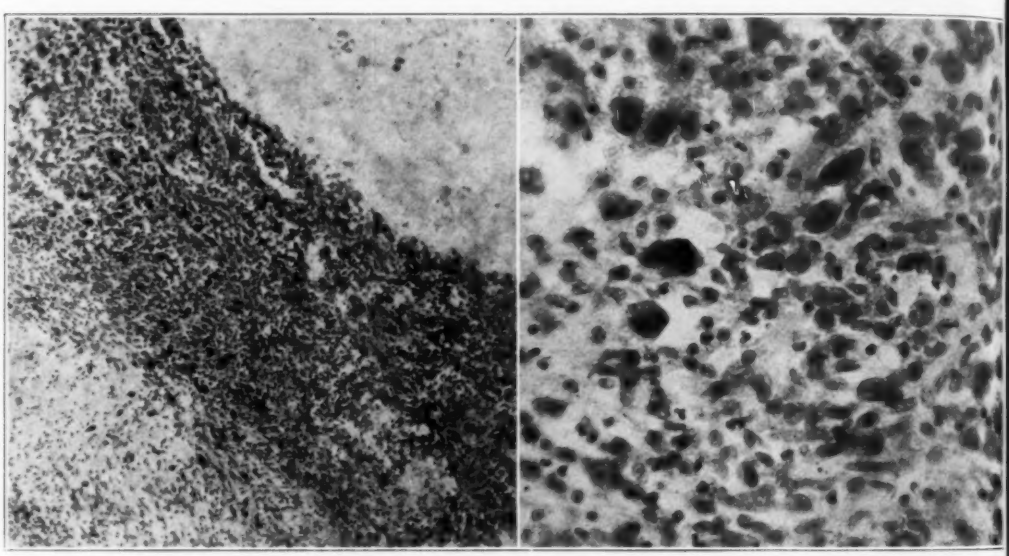

Fig. 90 (P. N. 37008).—Low and high power photomicrograph indicating the histologic structure of the tumor shown in figure 89. The tissue is very vascular, contains many abortive osteoblasts and resembles microscopically an osteolytic form of osteogenic sarcoma.

is in keeping with the general rule that the higher the state of differentiation in the neoplastic tissue, the less malignant is the clinical course.

VARIANTS OF THE SCLEROSING FORM OF OSTEOGENIC SARCOMA

While the predominant microscopic picture described for the sclerosing form of osteogenic sarcoma did not include cartilage or the malignant spindle cell with abortive osteoblasts, typical of the osteolytic type of sarcoma, cartilaginous tissue and a vascular tissue of malignant spindle and round cells may appear in periosteal sarcoma belonging to this main group.

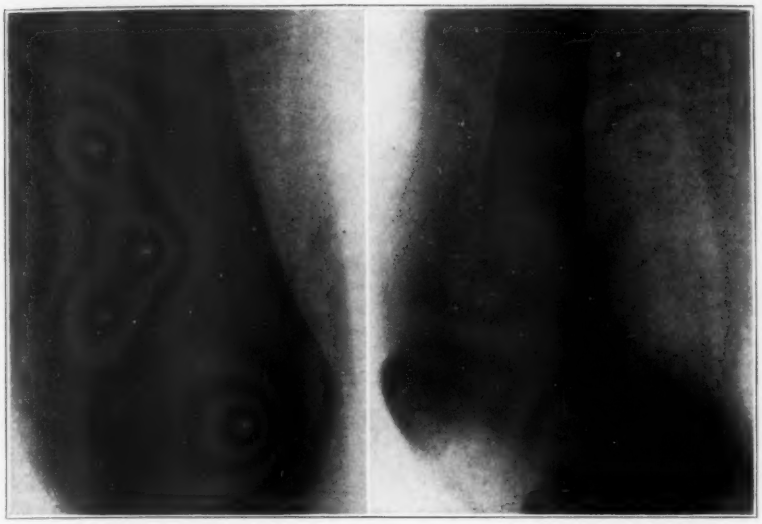

Fig. 91 (P. N. 27852).—A case of early sclerosing sarcoma classed as a mixed spindle and round cell variant. There is a characteristic roentgenographic appearance. The bulk of the tumor is subperiosteal and of a translucent appearance but secondary bone destruction has occurred in the marrow cavity.

Fig. 92 (P. N. 27852).—The gross specimen of the case shown in figure 91 which emphasizes the white, fibrous and osteoid substance of the tumor mass and the central hemorrhagic cavity opened up in cancellous bone which is typical for osteolytic sarcoma.

Fig. 93 (P. N. 27852).—The photomicrograph depicts spindle cells and early osteoblasts embedded in a pre-osteoid substance, indicating an early stage of ossification. (Same case illustrated in figures 91 and 92.)

About one case in five of the sclerosing form of sarcoma may show, under the microscope, small islands of cartilage being converted directly into an osteoid state. The presence of this cartilage is readily explained by the fact that the periosteal tissue from which the neoplasm arises is only a further stage in the development of the primitive perichondrium. Most of this periosteum, it is true, has lost the power to form cartilage at the time when these growths arise, but some of the more undiffer-

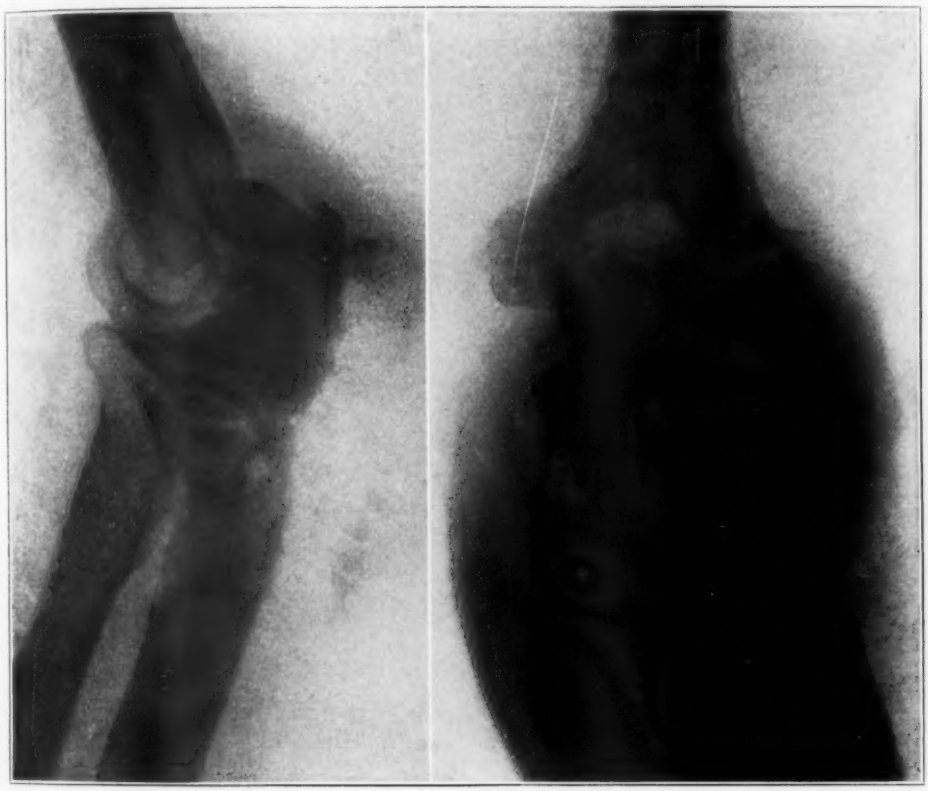

Fig. 94 (P. N. 28352).—Roentgenogram showing a fracture of the right ulna in a white man, aged 67, in which sclerosing sarcoma is arising in the callus. The fracture occurred one year previous to the symptoms of tumor formation. The patient died of metastases two and one-half years after amputation at the shoulder girdle.

entiated cells must persist and take part in the new growth. I do not believe that the chondral substance is to be accounted for on the basis of atavism or dedifferentiation on the part of portions of the periosteal tissue. From the standpoint of the clinician, the inclusion of small areas of cartilage in these growths is negligible. It affects in no way the roent-

genologic picture, nor is the prognosis influenced as far as can be determined from the clinical follow-up (figs. 85, 86, 87 and 88).

The mixed spindle and round cell variant of sclerosing, osteogenic sarcoma is worthy of more important consideration. It presents a predominantly bone-destructive appearance in the roentgenogram and coincides from a microscopic and prognostic standpoint with the osteolytic variety of osteogenic sarcoma. For this reason, in the tables it has been included with the osteolytic cases which are central in origin,

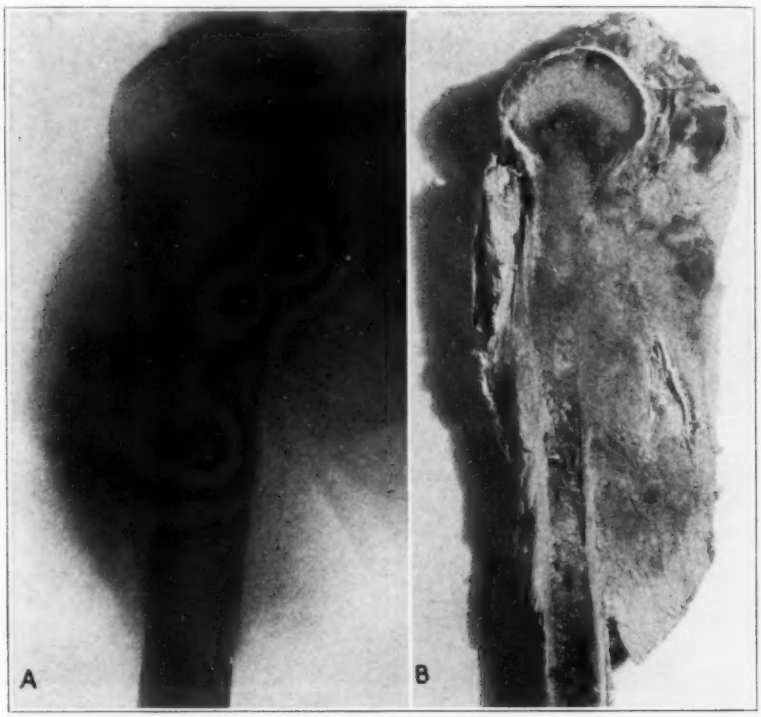

Fig. 95 (P. N. 36014).—A case of myositis ossificans undergoing secondary change into sclerosing osteogenic sarcoma in a white man, aged 28. *A*, taken in October, 1923, depicts the formation of new bone of a laminated character in the soft parts, typical of myositis ossificans traumatica, but in addition there is periosteal reaction indicating early malignancy. *B* shows the specimen amputated in July, 1926. The picture shows a fully developed sclerosing sarcoma which has infiltrated the marrow cavity.

although this variant itself must be conceded to be periosteal in its origin. There is no satisfactory way to classify this small group of lesions clinically (seven cases), since no matter how they are looked on they constitute a confusing exception. In the roentgenogram (figs. 89 and 91), they resemble a primary chondrosarcoma. In the gross and micro-

scopic specimens (figs. 90 and 92), they duplicate features of the osteolytic variety of tumor, and from a histogenetic standpoint they are closely allied with the sclerosing form (fig. 93). These tumors show an activity in primitive connective tissue of the periosteum, and although osteoid substance is produced that is midway between the osteolytic and sclerosing forms, the major portion of the tumor does not achieve a highly differentiated stage of osseous production.

Considering the twofold method of achieving bone in the skeleton, either from precartilaginous connective tissue, through cartilage to bone or from pre-osseous connective tissue directly to bone, it is readily understandable that a neoplasm exhibiting a highly differentiated state of ossification may retain remnants indicating a beginning in either the

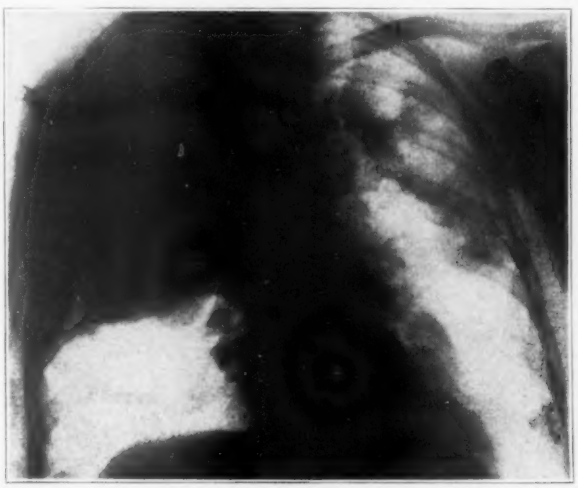

Fig. 96 (P. N. 36014).—Roentgenogram showing consolidation of the upper right side of the chest by tumor metastases, occurring in March, 1929, in the same case shown in figure 95.

more primitive precartilaginous or the pre-osseous state. On this basis, the areas of cartilage or mixed spindle and round cells found in sclerosing osteogenic sarcoma may be accounted for.

Secondary Sclerosing Sarcoma.—The clinical data just reviewed indicate that the usual sclerosing osteogenic sarcoma, whether typical or representing one of the variant forms described, arises de novo during the active period of growth of the skeleton. Practically all of the patients are between 15 and 35 years. There are, however, a few exceptions (four among seventy-eight cases), patients who are beyond the period of growth, and the inference is that the malignancy is secondary to an original primary and benign lesion.

This is definitely indicated by the data in one of the cases. In this instance, a white man, aged 67 (fig. 94), had fractured his right elbow one year previously. The roentgenogram showed a distinct ununited fracture with diffuse callous formation about the upper end of the ulna. In this callous formation a secondary malignant change occurred, and the patient died of metastases two and a half years after an amputation at the shoulder girdle.

Fig. 97 (P. N. 36014).—Photomicrograph showing malignant new bone in the case illustrated in figures 95 and 96.

In another case, a white woman, aged 38, complained of acute pain in the left side of the chest which was more intense on coughing. A brace was applied to the chest, roentgen therapy was given, and the lesion became apparently better. A year later the symptoms recurred, and a roentgenogram revealed an osteogenic sarcoma arising over the fourth rib in the axillary line. Although the examination was performed elsewhere and an inquiry was not made in regard to trauma, the history

suggests that this was apparently another instance of secondary sarcoma arising in the callus of a fracture.

Two other instances of secondary sclerosing osteogenic sarcoma in patients 28 and 34 years of age, respectively, are recorded in the laboratory. Both of these arose in a previously benign myositis ossificans and are shown in the accompanying illustrations (figs. 95 to 99).

Fig. 98 (P. N. 36014).—A portion of a metastatic nodule in the chest removed at autopsy. The patient died in July, 1929, six years after the original observation. (Same case as shown in figures 95 to 97.)

These proved instances of sclerosing, osteogenic sarcoma arising secondarily to benign lesions are in keeping with the evidence studied in regard to the other forms of osteogenic sarcoma. Both chondrosarcoma and the osteolytic varieties may arise as primary or secondary lesions, and to the sclerosing form must also be ascribed such possibilities.

CONCLUSIONS CONCERNING THE FIBRO-OSSEOUS FORMS OF OSTEOGENIC SARCOMA

In contrast to the chondral forms of osteogenic sarcoma, the fibro-osseous forms just discussed may achieve from the histogenetic standpoint a high degree of cellular differentiation, so that a relatively mature product of ossification represents the end-point of the series. This end-point, the sclerosing type of osteogenic sarcoma, is the least malignant of all the neoplasms discussed here and presents a fair degree

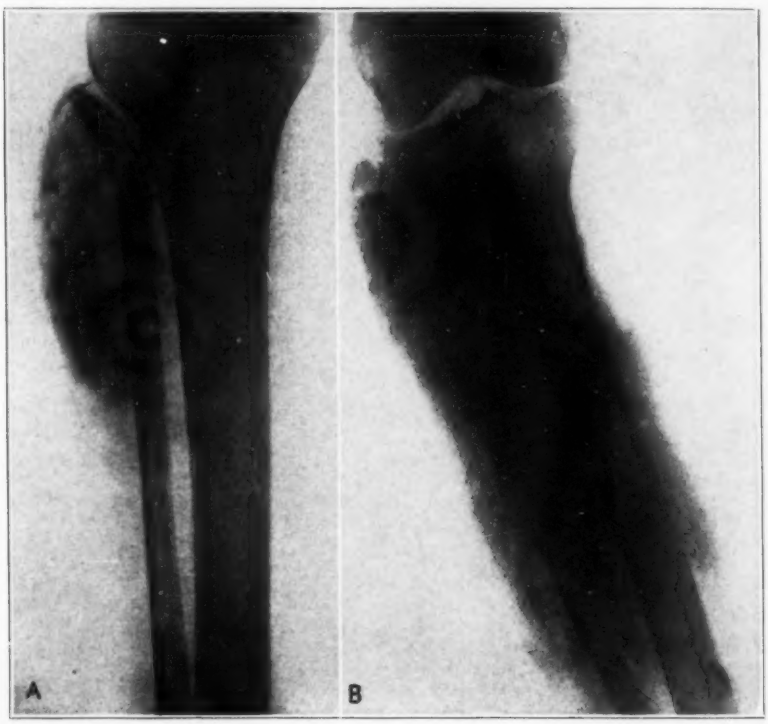

Fig. 99 (P. N. 27702).—A case of osteogenic sarcoma developing in myositis ossificans about the upper end of the fibula in a white woman, aged 34. *A*, taken in October, 1919, shows the ossifying periosteal mass with signs of malignant change. *B* shows the recurrent malignant growth in October, 1922, three years after a resection of the upper third of the fibula. This patient is living in 1931, eight years following an amputation for the recurrence. This case was reported by Paul (ARCH. SURG. **10**:185 [Jan.] 1925).

of curability. From a microscopic standpoint, therefore, these tumors may be definitely graded, the more mature cell forms being the least malignant. As in the chondral forms of sarcoma, the age of the patient is also a factor in the degree of malignancy, and among the osteolytic types of the fibro-osseous group it has been shown that the patients who

are cured are usually adults; on etiologic grounds there is reason to believe that secondary malignant change rather than a primary sarcoma was present in these successfully treated lesions. In this respect the osteolytic type of sarcoma presents a form that closely parallels secondary chondromyxosarcoma. In the more highly differentiated sclerosing sarcoma, age is not a striking factor unless the secondary form of malignancy, which is rare in this group, is present.

Separation of these fibro-osseous sarcomas into separate histogenetic types and the placing of the chondral forms likewise on an individual pathologic basis bring out forcibly the relation of these sarcomas to the processes of osseous development. It can be concluded from the analysis herein presented that a different type of tumor is possible for each phase of the histogenesis of the bone, emphasizing in a forceful way that the origin of these growths is intimately connected with the developmental steps in osteogenesis.

TABLE 6.—*Results in One Hundred and Sixty Fibro-Osseous Sarcomas*

	Sclerosing	Osteolytic
Total	73	87
Lost	5	6
Total followed	68	81
Followed over five years	55	63
Well over five years	17	4
Per cent of five year cures	31	6

CONCLUSIONS AND CLINICAL APPLICATIONS

The separation of osteogenic sarcoma into separate forms based on the individual phases of osteogenesis involved is not a theoretical attempt to arrive at the etiology of sarcoma, but is a serious endeavor to comprehend the behavior of these growths in their clinical aspects, although it cannot be denied that this analysis sheds a decided light on the nature of the malignant process in bone.

In summarizing some of the more important conclusions derived from this study, it is therefore advantageous to focus attention on the outstanding clinical applications.

Significance of a Protracted History.—The current conception of the typical sarcomatous history met with in patients suffering with malignant disease of the bone is in need of definite revision. A youthful patient and a brief acute clinical course are not indispensible to the diagnosis, and it can no longer be claimed that a prolonged history and advanced age rule out this dread disease. It has been shown that there are definite types of osteogenic sarcoma which arise in adults who may give a story of a preceding trauma dating back two to twenty-five years.

These are cases of secondary chondromyxosarcoma arising at the site of an exostosis or benign central chondroma, the osteolytic sarcoma which arises centrally in adults with an obscure complaint at the site of the malignant change, or the secondary sclerosing forms following on myositis ossificans and in callus after fracture. In these cases the unusual clinical aspects can be explained on the basis of a sarcoma arising from a previously benign condition, which either harbors undifferentiated embryonic tissue or is the seat of a chronic unhealed lesion. The clinician, therefore, must be on the lookout for these secondary malignant forms of osteogenic tumors, which in the roentgenograms are central bone-destructive lesions of an infiltrative type (arising in a bone which gives evidence of a previous exostosis, an expansile deformity caused by central chondroma or an old unhealed site following infection or trauma) or invasive periosteal growths (following on Paget's osteitis deformans, myositis ossificans or callus formation). While these tumors are definitely sarcomatous, they offer a better prognosis than the primarily malignant osteogenic tumors, and in grading constitute a distinct group.

Interpretation of Roentgenograms.—The fundamental basis of interpreting lesions of the bone in the x-ray film is also in need of revision. There is too much overlap in the roentgenologic picture between benign and malignant conditions if one looks on the film as presenting only the configuration of the result of the disease process. It is necessary to pass beyond the reliance placed on mere configuration and analyze the film as a dynamic record of both normal osteogenesis and a malignant perversion of some phase of this osteogenesis. Thus, in primary chondrosarcoma occurring in youthful patients, the sites of bony tubercles and of tendinous attachments thereto must be looked on as a zone of active growth in which the osseous portion of the tubercle is in balance with the precartilaginous portion of the tendon. When both proliferate, producing an osseous pedicle in bone and a cartilaginous cap in the tendon, the normal is exaggerated but the balance is still maintained, and the lesion is a benign exostosis. When the primitive cartilaginous portion only proliferates as a translucent periosteal shadow, the lesion is a primary chondrosarcoma. When the equilibrium reached in the exostosis is overthrown at a later date in a similar manner by precartilaginous tissue, the result is a secondary chondrosarcoma. From a similar point of view areas of destruction about a persisting epiphyseal line in a youthful patient must be regarded in relation to the active growth zone at this point, and the possibility of a chondroblastic sarcoma considered. Throughout the growth period lesions of the metaphysis that escape beyond the cortical shell must be looked on with suspicion, and their relationship to sclerosing osteogenic sarcoma ascertained. The

osteolytic form of sarcoma must be thought of as a possibility when the cancellous bone in this metaphyseal region is involved by a destructive process, and a cavity in the bone opened up which escapes beyond the cortex. The coincidence of a separate type of osteogenic sarcoma with an individual zone of osseous development explains the variability of the roentgen finding in this group of neoplasms. The fact that osteogenic sarcoma may sometimes give rise to a central osteolytic lesion in the x-ray film, and in other instances sclerose the marrow cavity; that under certain conditions it may be predominantly a periosteal lesion, and again be predominantly central, emphasizes the necessity of interpreting the roentgenogram in relation to the phase of osteogenesis involved by the tumor rather than attributing these contrasting pictures to chance or to an indefinable complexity.

Coordination of Clinical and Pathologic Findings.—A more complete coordination between the clinical and pathologic picture is made possible by this factoring of the various forms of osteogenic sarcoma. The pathologic findings of giant cells in the central destructive forms of sarcoma of either the chondroblastic or osteolytic types need no longer be a source of confusion to the surgeon or the pathologist who understands that secondary invasion by the giant cells is to be expected as a subordinate phase to either cartilaginous proliferation in chondroblastic sarcoma or to the laying down of poorly formed osteoid substance among the large malignant spindle and round cells of osteolytic sarcoma. There is thus no need to try to stretch the conception of benign giant cell tumor to include these malignant phases that are in reality primarily sarcomatous.

The malignancy of chondromyxomatous tumors in which myxoma and actively proliferating early connective tissue predominate is on a surer footing when the idea that myxoma is a degeneration product of cartilage is abandoned and when this precartilaginous tissue inappropriately referred to as myxoma is viewed instead as the mother substance of these growths. It is also helpful to know by the same token that the cartilage in these growths is the result and not the progenitor of the myxomatous tissue.

The pleomorphic forms of osteoblasts scattered among osteoid substance and spindle cells without relation to spicule formation serve to set apart the production of malignant bone of sclerosing sarcoma and to differentiate it from normal reactive bone laid down in spicule formation in benign inflammatory conditions and osteitis fibrosa. The close relationship of the histology of this tumor to such normal osseous production at the same time gives a key to the better prognosis among patients with this sclerosing neoplasm as compared with sarcoma in bone of other forms.

Grading of Osteogenic Sarcoma.—For the first time a fairly reliable grading of the degree of malignancy of sarcomas of the osteogenic group is made possible, and the prognosis rendered more than a shrewd guess. The clinical aspects of the lesion, including the roentgenogram, may be used in conjunction with the microscopic picture to grade these neoplasms. When the most advantageous treatment is used, from 5 to 10 per cent of permanent cures is the base line. This is the minimum opportunity for escape from fatality whether the lesion is a chondromyxosarcoma, a chondroblastic sarcoma or an osteolytic sarcoma. From this minimum the chances of cure are increased fivefold, if the lesion arises as a secondary malignant change or if the tissue of origin is of the highly differentiated sclerosing form. The higher the age of the patient and the more protracted the clinical course, the more likelihood is there of a secondary and hence more benign type of sarcoma. This likelihood is strengthened when the roentgenogram shows evidence of a pre-existing exostosis or chondroma in a chondromyxosarcoma or a central bone-destructive growth of the osteolytic type in an adult over 30, and is confirmed when the microscopic picture shows a tumor in which myxoma and necrotic cartilage predominate, or when the tumor contains malignant spindle and round cells with giant cells indicative of the osteolytic type. In the sclerosing form the shaggy sun-ray picture in the x-ray film and the predominance of osteoblasts and osteoid substance under the microscope establishes the better prognosis.

Indications for Irradiation.—Deep roentgen and radium therapy have now taken their places as established methods of treatment in malignant disease, and the question of whether or not a neoplasm is histologically of a proved radiosensitive type is an extremely important consideration. Taken as a group, it is impossible to state whether or not the osteogenic sarcomas are or are not radiosensitive, and unless these tumors have been analyzed on a histogenetic basis, this matter cannot be decided. From the present study, however, it can be concluded that the forms of osteogenic sarcoma arising from precartilaginous connective tissue (chondromyxosarcoma) and cartilage (chondroblastic sarcoma) show definite evidence of being relatively radiosensitive, and those tumors of the fibro-osseous series are relatively radioresistant. This is in keeping with the general rule that all neoplasms arising in tissue of an undifferentiated embryonal type are prone to yield to radiotherapy, whereas those involving a more highly differentiated group of cell forms are usually refractory to this mode of treatment. At the present time, radium therapy has achieved better results than deep roentgen therapy in the chondral forms of sarcoma. A review of the cases in which cure has been obtained does not show any difference in the ultimate outcome of cases in which irradiation has been used preoperatively and those in which it has been used postoperatively.

It is important to emphasize, however, that in none of the forms of osteogenic sarcoma can it be proved that irradiation alone suffices for a permanent cure. When irradiation has been tried over a period of one month as the initial form of treatment without definite and striking results, surgical measures should be promptly instituted.

Etiology.—The relationship of tumors of the bone to various phases of osteogenesis herein set forth correlates the age of the patient and the site of the tumor characteristic of the individual forms of osteogenic sarcoma with the time and locality of normal histogenetic processes occurring in the various growth zones of the skeleton. That such a correlation is not the result of mere coincidence is demonstrated by the histologic composition of the neoplasm itself, which duplicates in epitome, although in a somewhat distorted manner, the normal order of developmental steps peculiar to the tissue from which it arises. It may be concluded, therefore, that a normal and active center of tissue differentiation constitutes a predisposing cause to the formation of tumor. This conception enlarges the insufficient embryonic theory of Cohnheim, recognizing that histogenesis in the tissue is not confined to the embryo, but occurs in all normal structures at various periods throughout life. This, however, does not detract from the veracity of the Cohnheim doctrine, for it has been shown in the secondary forms of osteogenic sarcoma that relatively undifferentiated tissue may be harbored in a benign neoplasm until late adult life, and affords independent of normal growth cycles the basis of subsequent tumor formation. Although a restricted age incidence and a characteristic localization is thus one of the fundamental attributes of a well defined neoplastic entity, a belated and less malignant tumor of the same histologic type may arise in more advanced age, as a secondary change to some benign growth.

An important corollary to this histogenetic conception of neoplasms is that the variety of etiologic factors proposed for malignancy—trauma, infection, chronic irritation, metabolic or endocrine imbalance, etc.—must be looked on as precipitating agents only for these new growths. The properties of the consequent neoplastic transformation are inherent in the tissue of origin rather than in the etiologic agent, and remain constant for a given tumor despite variability in the factors of causation. The developmental steps concerned in the construction and growth, in the maturity and eventual senescence of bodily tissues and organs from this standpoint constitute more fruitful fields for investigation into the nature of malignancy than do the various carcinogenic agents of a chemical or bacterial nature so diligently searched for in many laboratories.

AVERTIN FLUID ANESTHESIA IN SURGERY*

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In general anesthesia the trend is directed toward an anesthetic agent that eliminates the psychic shock and diminishes to the largest possible extent any undesirable after-effects as feared with the classic anesthetics given by inhalation.

Of new anesthetic agents introduced into clinical practice, avertin, or tribromethanol, appears most promising. The European literature reports about 400,000 cases since its introduction three years ago. In this paper a résumé of available data on its pharmacology and clinical uses is made, as well as a report of 100 cases in which avertin fluid was used.

REVIEW OF LITERATURE

Chemical and Physical Properties.—Avertin is tribromethanol (Willstaetter and Duisberg), a white crystalline substance, which readily sublimes and is soluble in water at 104 F. up to 3.5 per cent. It must be protected against light and heat. The avertin amylene hydrate solution, commercially called avertin fluid, contains 1 Gm. of avertin and 0.5 cc. of amylene hydrate in 1 cc. of solution. Amylene hydrate is a tertiary alcohol with this formula: $(CH_3)_2C_2H_5COH$. Chemically, it is dimethylethylcarbinol. It is a colorless, oily fluid, soluble in water, at a ratio of 1:8, with an odor resembling paraldehyde. According to Grossmann, amylene hydrate has the property of dissolving avertin in high concentrations, and is itself readily soluble in water.

Solutions of avertin must be prepared at temperatures between 95 and 100 F. At higher temperatures hydrobromic acid and dibromacetaldehyde are formed. The former reacts neutral to congo red, the latter, with hydrolysis present, reacts distinctly acid to the indicator.

Pharmacology.—Dosage: Experimentation by Eichholtz shows that the response to avertin in different species varies considerably. In cats, anesthesia is obtained following oral administration of 0.15 Gm. high as from 0.5 to 1.6 Gm. per kilogram of body weight to produce anesthesia. Administration by rectum produces similar variations;

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* From the Surgical Service of the Evangelical Deaconess Hospital.

mice require only from 0.15 to 0.18 Gm. per kilogram, whereas dogs require 0.15 Gm. per kilogram of body weight to produce deep anesthesia. The lethal dose in animals is from 75 to 100 per cent in excess of the anesthetic dose. In white mice no tolerance for the drug was noted, even after the administration of daily rectal doses from 0.4 to 0.5 Gm. for seven weeks. The pathologic examination of tissues was negative.

Absorption: According to Straub, one half of the 3 per cent avertin solution (0.15 mg.) per kilogram of body weight is absorbed after ten minutes; twenty minutes later three fourths of the avertin is absorbed. He has shown that 86 per cent of the solution is assimilated twenty-five minutes after administration of the enema. The rest remains in the rectum for hours, during which time it is slowly absorbed. Straub found from 5 to 10 per cent in the rectum, after two hours. The concentration of avertin in the blood rises to 6 or 9 mg. per hundred cubic centimeters in the first twenty minutes. This concentration falls rapidly to 3 mg. and then slowly to 0.15 mg. per hundred cubic centimeters when awakening takes place. Experiments show that the permeability of the intestinal wall decreases markedly after the first administration of avertin solution.

Excretion: By its combining with glycuronic acid the drug is eliminated through the kidney (Endoh). Straub recovered from 70 to 80 per cent of the drug in the first forty-eight hours and 91 per cent in six days. He also showed that no bromine was eliminated through the feces or perspiration, and none in the urine as a bromide, which demonstrated that the drug was not hydrolyzed in the body.

Effect on Circulation: Blood containing 0.12 Gm. of avertin per hundred cubic centimeters gave no alteration in either strength or stroke volume of the heart, and paralysis was observed only in much higher concentrations. Parsons claimed that avertin is one-sixteenth as toxic as chloroform. In men, as found by Franken and Schürmayer, there was a diminished volume of circulating blood as much as from 20 to 25 per cent due to vasomotor depression and an accompanying drop in blood pressure. No action on the heart muscle was found.

Effect on Respiration: Experiments on rabbits following rectal administration of avertin showed a decided diminution in respiratory rate and minute volume. These reached their maximum intensity in the first ten minutes, and gradually returned to normal. Eichholtz, however, stated that the respiratory rate was decreased; the minute volume, however, remained the same. These disturbances are central in origin; peripheral nerve and vagus actions are not known.

Effects on Blood Chemistry: The effect on the blood chemistry is only partly investigated. In human beings the hydrogen ion concentration remains the same. The blood sugar rises sharply, but returns to

normal in from six to twenty-four hours after induction of anesthesia in animals. The glycogen in the liver is depleted. Preliminary ligation of the veins of the liver prevents the rise in blood sugar, thus proving that the liver is a factor in absorption and detoxication. The alkali reserve remained normal. Like ether, tribromethanol causes a decrease of calcium in the blood. The p_H, according to Wymer, is decreased even for as long as twenty-four hours.

Margin of Safety: Kärber and Lendle showed that surgical anesthesia was obtained in rabbits by rectal administration of 0.35 Gm. per kilogram, whereas fatal doses of the drug are from 0.55 to 0.6 Gm. per kilogram of body weight. Therefore, it appears that the anesthetic dose is approximately 65 per cent of the fatal dose.

Effect of Repeated Use: Repeated administration of avertin over a long period of time produced no injury to the internal organs of animals. A dose of from 400 to 500 mg. per kilogram was given rectally to white mice on one hundred successive days with no deleterious effects on any of the abdominal viscera. Some of the animals became pregnant during this time and had healthy offspring. On the other hand, ether and chloroform were not nearly so well tolerated, the animals succumbing after a few tests.

CLINICAL APPLICATION

Preanesthetic Medication.—The general plan of preanesthetic technic among the German clinicians is relatively uniform. A cleansing enema, or a mild cathartic, is given the night before the operation. The patient is put on a liquid diet. Some somnifacient, such as dial or barbital, is given the evening before. The preoperative hypodermic injection of morphine-scopolamine or papaverine is given about one and one-half hours prior to the administration of tribromethanol. Martin elaborated the technic by advocating the administration of fractional doses of scopolamine and a morphine-narcotic meconate mixture with fractional doses of avertin, using age as a basis. He reported full narcosis in 96 per cent, the cases including all types of surgical procedures.

Preparation of Solution.—Tribromethanol is usually administered in a 2.5 per cent solution. The solid avertin is dissolved in warm water, the temperature of which does not exceed 104 F. The solution hydrolyzes at from 110 to 115 F., giving off hydrobromic acid and dibromacetaldehyde, which reacts distinctly acid to congo red.

By using avertin fluid the technic is simplified. The amount is measured in a Luer syringe or a graduated pipet, the average dose being about 0.1 Gm. per kilogram of body weight. Moerin stated that doses in excess of 0.15 Gm. per kilogram are too high for general use. He suggested giving a dose of 0.1 Gm. of avertin fluid per kilogram, and if the patient is sensitive to pain after fifteen minutes, an addition of 0.25

Gm. per kilogram is given. Various solvents such as physiologic solution of sodium chloride, 1 per cent salep mucilage, gum acacia or milk have been used; however, most authors agree that distilled water is least cumbersome and causes less intestinal irritation.

Dosage.—The dosage of tribromethanol has varied from 0.08 to 0.2 Gm. per kilogram of body weight. In using the solid avertin, doses as high as from 0.15 to 0.175 Gm. per kilogram have been given. However, the general dosage that can be regarded as safe is 0.125 Gm.

In using avertin fluid the dosage is less, 0.1 Gm. per kilogram corresponding to 0.125 of solid avertin. This has been proved clinically by Grossmann in a report of 215 cases. Most fatalities or excessive decreases in blood pressure have been noted only in those cases in which the dosage was in excess of 0.125 Gm. for avertin fluid and 0.150 Gm. for the solid avertin.

Sievers reported 1,200 cases in children who received from 0.125 to 0.150 Gm. per kilogram of body weight in a 3 per cent solution. No untoward effects were noted. If necessary, avertin was supplemented with a small amount of ether, as particularly advocated by Ebhardt and Anschütz.

Depth and Duration of Anesthesia.—The depth and duration of rectal administration of avertin vary greatly in different persons. Children show a marked tolerance to avertin, and, as previously stated, tolerate larger doses of the anesthetic. In administration of dosages based on weight, only 30 per cent of the children were completely anesthetized, while in adults given the same relative dosage, from 70 to 80 per cent were surgically anesthetized. The patient sleeps from three to five hours, depending on the type of patient and the dosage. No excitement stage has been noted by any of the German clinicians. Nausea and vomiting are extremely rare.

Dangers and Remedies.—The principal dangers in the use of tribromethanol anesthesia, aside from injections of a hydrolyzed solution, which causes irritation and slough of rectal mucosa, are respiratory and circulatory changes and impairment of the excretory organs.

Respiratory: Impairment of respiration due to the action on the respiratory center is the greatest danger of avertin fluid anesthesia. In case of impairment, carbon dioxide is most efficacious (Martin), and in mild cases of impairment, lobeline. This drug is effective; however, in grave respiratory embarrassment it has proved to be a failure.

Dreessen reported a death occurring in a woman 68 years of age with a blood pressure of 220 systolic and 170 diastolic and with chronic nephritis. A radical operation for carcinoma mammae was contemplated. One-tenth gram per kilogram of body weight in a 2.5 per cent solution was given rectally. Five minutes after the beginning of the instillation, respirations ceased. The pulse was not palpable. Lobeline

and artificial respiration relieved the condition. Twenty-five minutes after the enema, the operation was begun, and the same collapse recurred. The remaining solution in the rectum was drawn off. Carbon dioxide and lobeline were ineffective, and the patient expired on the operating table. No autopsy was obtained.

In accordance with the experience of Killian, coramine "ciba" given intravenously up to 4 cc. exerted a marked stimulation of the rate of respiration, thereby bringing about a rapid awakening from avertin narcosis. Thus coramine proved to be the most valuable adjunct in combating respiratory and circulatory failure, presumably by its rapid action on the medulla oblongata.

Circulatory: Prophylactic administration of ephedrine is of value and proves very effective in those cases in which there is a marked drop in blood pressure. Pribram showed that thyroxine raises the blood pressure and shortens narcosis. In one case he administered 1 cc. of thyroxine to a patient whose blood pressure had fallen 70 mm. of mercury and in whom the pulse was not palpable. Thyroxine raised the blood pressure, and the patient was fully awake in two hours.

Urinary: Urinary complications are rare. Transient albuminuria, occasional erythrocytes and granular casts have been noted.

Kallmann reported the case of a healthy patient who was given 0.125 Gm. per kilogram for an Alexander-Adams operation. Barbital, 0.5 Gm., was given the night before and repeated two hours before operation. As a preoperative hypodermic, 0.02 Gm. of pantopon was given. The patient expired seventeen and one-half hours after operation. Autopsy revealed fatty infiltration of liver cells. The urinary bladder was empty. The kidney showed fatty infiltration of the tubuli contorti. Kallmann assumed that damage to the kidney was caused by avertin. Death was probably due to the barbital, pantopon and avertin preparation, which in the opinion of Anschütz is a faulty preparation.

Contraindications for the use of avertin are: 1. Severe liver damage. The matter of liver damage by avertin is still under discussion. Heinecke maintained that postoperative prophylactic feeding of dextrose makes avertin narcosis safe even in diseases of the liver. Cholecystectomy was done by Heinecke on a patient under avertin, aged 42 years, who had symptoms of common duct obstruction and severe jaundice over a period of fourteen years. The dose given was 0.15 Gm. per kilogram of body weight. The patient died on the fifth day with mania and an intense jaundice. Death could probably have been avoided by using a smaller dose and prophylactic preoperative administration of dextrose and insulin.

2. Severe kidney damage.

3. Chronic ileus with ensuing acidosis, dehydration and shock. If these adverse conditions can be overcome by administration of dextrose

and fluids intravenously, avertin can be given with impunity; however, in reduced dosages.

4. Severe cachexia due to malignant growths. In these cases the dosage must be reduced.

According to Anschütz, the relative danger and mortality of the different anesthetics in the hands of experienced men are as follows:

(*a*) 1 death in 10,000 avertin (Specht)
(*b*) 1 death in 5,112 ether (Gurlt)
(*c*) 1 death in 2,075 chloroform (Schmieden and Sebening)
(*d*) 1 death in 2,524 spinal (Strauss)
(*e*) 1 death in 343 splanchnic (Mecker)

CLINICAL INVESTIGATION OF AVERTIN FLUID AND TECHNIC OF ADMINISTRATION

In November, 1930, we began the use of avertin fluid for anesthesia at the Deaconess Hospital. Our original technic was the one used for solid avertin, gathered from German surgical reports. Since that time we have almost completely revised our original method, including preoperative and postoperative care for the patient who is to receive rectal administration of avertin fluid.

Preparation of Patient.—In the afternoon preceding the day of operation the patient is weighed and given a cleansing enema, either a soap suds or a salt solution enema. At bedtime some type of somnifacient, as dial, is administered. We do not advocate the use of narcotics on the evening preceding operation unless the patient has considerable pain. Oral hygiene is effected by the use of a mouth wash. As a preanesthetic medication given by hypodermic injection one and one-half hours before operation, we have used ⅓ grain (22 mg.) of pantopium hydrochloride[1] and 1/100 grain (0.6 mg.) of scopolamine as a routine measure in patients over the ages of 17 to 18 years. In persons below these ages, the dosage is decreased to ⅙ grain (11 mg.) of pantopium hydrochloride and 1/200 grain (0.3 mg.) of scopolamine. No preoperative narcotic is given to children under 10 years of age. In all preanesthetic medications given by hypodermic injection, we have used scopolamine in ampule form, and we have found this preparation to be the most stable and to cause less depression of the respiratory center. Naturally, the preoperative medication did not produce the same effects in all persons. Some stated that they were only slightly drowsy, while the greater number showed no appreciable changes. However, we did not

1. This preparation was purchased under the brand name of Pantopon. Since this work was done the Council on Pharmacy and Chemistry has issued a report rejecting Pantopon (J. A. M. A. **97**:1001 [Oct. 3] 1931) for conflict with certain of its rules.

use this as a guide for either increasing or decreasing the dose of avertin fluid. In all cases we administered the same minimum dose of 0.1 Gm. per kilogram of body weight.

Preparation of Solutions.—In all our cases we used avertin in amylene hydrate, or avertin fluid, as it is called commercially. Distilled water sufficient to make a 2.5 per cent solution in an Erlenmeyer flask is heated on an asbestos plate over a gas flame to a temperature between 100 and 104 F. The computed amount of avertin fluid according to weight is measured with a graduated syringe, or pipet, and added to the heated distilled water. By thorough shaking, the avertin fluid disseminates itself, and the result is a clear homogeneous fluid.

One or two cubic centimeters is placed in a small container, and a drop of congo red is added. The mixture remains pink, or neutral, to congo red. We have not, up to the present time, had to discard any of the mixtures due to positive reaction to the indicator. We found that avertin fluid is much more readily miscible in heated distilled water than in nonheated water. The solution is administered immediately after mixing.

Dosage.—Persons over 17 years of age were given 1 cc. or 0.1 Gm. of avertin fluid per kilogram of body weight, while in children the dosage varied from 0.125 to 0.150 Gm. per kilogram of body weight. Distilled water is added to make a 2.5 per cent solution. In obese persons, in severe cachexia and dehydration and in severe liver damage, as advocated by German clinicians, we reduced the dose to 0.08 or 0.09 Gm. per kilogram, depending on the condition of the patient.

Method of Administration.—The blood pressure apparatus is placed on the patient's arm before instillation of the solution, and the blood pressure and the pulse are recorded. The solution is administered one-half hour before operation, in bed, with the patient lying on his left side and in a moderate Trendelenburg position. This is effected by turning up the foot of the bed, or by placing pillows under the hips of the patient. A soft rubber catheter is inserted into the rectum for about 3 or 4 inches. A long-necked bulb syringe is placed into the end of the catheter, and the solution is allowed to gravitate into the rectum. In those cases in which the solution did not gravitate, we have used the bulb syringe, or blown the solution through the funnel. The length of time used for the instillation was usually from five to eight minutes. The remainder of the solution in the catheter is forced into the rectum as previously described, and the catheter is withdrawn while blowing into the funnel. We have not encountered any loss of solution.

Supplementary Anesthesia.—Local anesthetic was used in but one case with good results.

In those cases in which the patient reacted, we have used nitrous oxide exclusively with extremely favorable results. The amount of nitrous oxide used was negligible in most cases, except when the operations lasted longer than two hours. We do not advocate additional doses of avertin solution because it entails too much inconvenience when the patient is draped, sterile, on the operating table. We agree with most American writers that in those cases in which full anesthesia is not obtained with avertin solution, a tangible anesthetic, preferably nitrous oxide in our experience, be used. We were never forced to supplement with ether to obtain relaxation in those cases in which avertin solution did not produce complete surgical anesthesia, providing 0.1 Gm. per kilogram was given.

In ten cases we attempted to prolong the effects of avertin fluid by preliminary administration of 3 grains (0.19 gm.) of sodium amytal by mouth, two hours before operation. We observed that in those cases the sodium amytal diminished the depth of anesthesia otherwise obtained with avertin fluid alone.

Management During and After Anesthesia.—From the time the solution is injected until complete recovery, the patient is under careful supervision. The anesthetic is given in the room, and the patient is taken to the operating room about twenty-five minutes after the beginning of the instillation. The anesthetist remains with the patient until after the operation, at which time an experienced nurse stays at his side. We do not advocate the insertion of an airway until the patient reaches the operating room, since the absorption is not sufficient to cause abolition of the pharyngeal reflex, and this is manifested by considerable coughing. Respiratory embarrassment early after instillation has not been noted by us. After the patient has been prepared on the operating table, the airway is inserted, and all patients have well tolerated the procedure. In those cases in which there is an excessive drop in blood pressure, and if it does not rise after the incision, we advocate the use of ephedrine sulphate; after the use of this drug we have noted an almost immediate rise. Diligent watching of the patient and frequent blood pressure readings should be particularly stressed.

After operation the patient is brought back to his room and the pharyngeal airway is allowed to remain in place until he attempts to expel it himself. A subcutaneous hyperdermoclysis of 1,000 cc. of physiologic solution of sodium chloride is given immediately, which procedure we have found to shorten narcosis from one to one and one-half hours. Intravenous medication, unless deemed necessary for combating surgical shock, has not been given. Pantopium hydrochloride, $\frac{1}{3}$ or $\frac{1}{6}$ grain, depending on the age of the patient, is administered by hypodermic injection as a routine measure for pain and restlessness, and we have found that only a few doses are required, because the anes-

thesia seems to allay pain for the first twelve hours. On awakening, the patient is given fluids by mouth, in quantities as are comfortably tolerated. Many patients have taken orange juice and broth on the day of operation.

Mortality.—In our series of cases there have been two mortalities, not directly attributable to avertin anesthesia. In both cases the patients came to the operating room in a dehydrated condition. They illustrate why many authors exclude avertin in cases of chronic ileus, on account of the existing dehydration with acidosis.

CASE 1.—A patient with a ruptured gastric ulcer was given 0.1 Gm. of avertin per kilogram of body weight. The clinical history was that of an ulcer of rather acute onset. The ulcer, as nearly as could be ascertained, had been perforated approximately twenty-eight hours, during which time there was coffee-ground vomitus. Examination revealed a well developed man, in severe shock, and pale; the extremities were cold and clammy. The abdomen had boardlike rigidity. On laparotomy, a large ruptured gastric ulcer was found on the lesser curvature. The stomach contents, including food, and digested blood clots were found in the abdominal cavity. The patient never rallied from the anesthesia and apparently succumbed to overwhelming shock and peritonitis, two hours after operation. No autopsy was performed.

CASE 2.—A patient with intestinal obstruction and annular carcinoma of the sigmoid had symptoms of obstruction of five days' duration. He had been vomiting two days. The abdomen was markedly distended. No results were obtained with enemas or cathartics. On examinations, the pupils were found to be unequal; they reacted sluggishly to light but reacted in accommodation. A diagnosis of syphilitic heart disease was made. The blood pressure reading was 135 systolic and 80 diastolic. On laparotomy, a large annular carcinoma was found at the first portion of the sigmoid, and the large and small bowel were markedly distended. A right pararectal colostomy was done. The patient, on returning from the operating room, was cyanotic; the pulse was weak and fast. Stimulants were administered intravenously, but to no avail. Two hours and thirty-five minutes after operation, the patient died.

Postmortem examination revealed the cause of death as follows: syphilitic endocarditis and myocarditis, chronic syphilitic aortitis and aspiration pneumonia.

OBSERVATIONS

Induction.—The patients who received rectal administration of avertin fluid seemed to fall into a normal sleep. Narcosis took place in from five to twelve minutes, and in all cases we attempted to use that much time for instillation so that on removal of the catheter the patient would not be stimulated. Some patients continued to talk during the instillation, but wtihin a few minutes the tongue would become thick, and later the response would be only a mumbling. The head and arms relaxed very soon, and the patient appeared as if in a deep slumber.

Vomiting persisted in the case of intestinal obstruction, even after instillation of the anesthetic and during the entire operation. The patient expired. Any other type of anesthesia would have affected the

patient in the same way. The aspiration of some of the vomitus probably accounts for the aspiration pneumonia and death after circulatory failure.

Pharyngeal reflexes are lost in from twenty to twenty-five minutes. Responses to skin stimuli are lost in approximately twenty-five minutes after instillation; however, some patients reacted slightly after the initial incision was made. This proved to be an embarrassment in operations on the skin, such as excision of varicose veins and perineorrhaphy. The pupils contracted in about ten minutes but reacted to light. In the greater number of cases the pupils dilated to half the maximum after skin incision or peritoneal stimulation; the respiratory volume was increased. Muscular relaxation for laparotomy was excellent, even in those cases in which full surgical anesthesia was not obtained.

Duration of Anesthesia; Recovery.—Narcosis with avertin fluid ranges from three to five hours. One patient with secondary anemia slept eight hours. We noted that approximately 20 per cent of our patients showed restlessness on awakening; however, this has been successfully controlled with a mixture of opium alkaloids. The remainder of the patients awoke as if from a natural sleep. In not a few instances the patients inquired whether they had been operated on. Pain seemed to be allayed the first eight to twelve hours. We are convinced that by elimination of the psychic shock, by the administration of a basic anesthesia such as avertin fluid, the recovery is markedly shortened. The early return to normal physiologic function of the vital organs by the intake of nourishment by mouth is a point that we consider paramount for early recoveries.

Coramine "ciba" given intravenously or intramuscularly up to 4 cc. shortened narcosis from 40 to 50 per cent. In a few instances after injection of coramine "ciba," the patients awoke within one hour.

Circulatory Effects.—There is an initial drop in blood pressure, of about 10 to 15 mm. of mercury, which soon rises to the normal level and remains there. In a few cases the blood pressure during operation has dropped 30 to 40 mm.; the administration of ephedrine sulphate readily brought the reading up to the normal level. A marked pallor, however only transient, was shown by some patients. This phenomenon may be what some writers termed vasomotor depression. The pulse did not show any appreciable changes either in volume or in rate per minute.

A patient with a marked secondary anemia, some poikilocytosis, anisocytosis and a hemoglobin of 45 per cent (Dare) was given avertin fluid. The narcosis was extremely deep, and the patient did not react until after eight hours, even though 700 cc. of 10 per cent dextrose solution was given intravenously. No ill effects were noted; the blood cells and hemoglobin, in fact, were increased two days after operation.

Blood counts after operation showed results comparable to any other type of anesthesia. Waters and Muehlberger reported that no consistent or significant changes occur in the blood chemistry. The rise in blood sugar with avertin fluid is less than in other types of anesthetics.

Respiratory Effects.—The respiratory rate per minute generally remained the same. The volume per minute of inspired and expired air was decreased about one-third. In the presence of an acute respiratory infection, avertin fluid should not be given. A patient developed an acute respiratory infection during the night, and avertin fluid was given the following morning. From the beginning of narcosis the patient coughed severely, was cyanotic and appeared asphyxiated; an airway was not tolerated. Carbon dioxide, oxygen, ephedrine and caffeine were given, with a subcutaneous injection of physiologic solution of sodium chloride. The narcosis was shortened to one hour; the operation was not performed. We have found that about 5 per cent of the patients who have had avertin fluid developed a cough on the second or third day. This phenomenon we attribute to the exhalation of amylene hydrate through the alveolar walls, thus acting as an irritant to the mucosa of the throat. This is readily controlled by codeine sulphate.

Gastro-Intestinal Effects.—Nausea is extremely rare, and vomiting is uncommon, excepting in those cases in which there was excessive manipulation of the gallbladder, its ducts, the duodenum and the stomach. Even in those cases in which vomiting occurred, the patients had only one or two emeses as compared to incessant vomiting, even for days, after operations in which inhalation anesthesia was used. The patients, in most cases, took liquids in abundance on the day of operation. Only one case of bleeding from the rectum, in a patient who had had hemorrhoids, came to our attention. In no other case have we noted any subjective symptomatology. A proctoscopic examination has not been done.

Genito-Urinary Effects.—The urinary changes postoperatively are comparable to those in any other type of anesthesia. Urinary suppression was not noted. In five cases erythrocytes appeared in the urine on the second day, and on repeated analyses was found to be only a transient phenomenon. In three cases hyaline casts appeared in the urine; a trace of albumin had been noted preoperatively. In five cases leukocytes appeared postoperatively. In the remainder of the cases the changes were not significant.

Central Nervous System; Psychic Effects.—In none of the patients who received avertin fluid by rectum have we noted any excitement stage immediately after instillation. By the combination with scopolamine we dispensed completely with the psychic shock and the aftermath of a terrifying experience. Approximately 25 per cent of the patients

showed restlessness on awakening; the administration of ⅓ grain of pantopium hydrochloride controlled this successfully at the onset. The patient awakens as if from a normal sleep. Postoperative psychoses have not been encountered.

SUMMARY

Avertin fluid given rectally to a patient with a preliminary administration of dial, pantopium hydrochloride and scopolamine leads to a natural sleep with complete surgical anesthesia in from 83 to 88 per cent of the cases, including all types of surgery. The psychic shock is completely eliminated.

In emergency cases with only an opium alkaloid preparation and scopolamine, surgical anesthesia was obtained in 75 per cent of the cases. In the remainder of the cases only a small amount of nitrous oxide was used and then only intermittently. We were never forced to use ether to obtain relaxation. The absence of headache and nausea and the rarity of vomiting are assets distinctive for this type of anesthesia.

Several hours of sleep after operation is very beneficial, and after the patient awakens, pain seems to be allayed the first ten to twelve hours.

Intravenous injection of coramine "ciba" shortens the duration of sleep without interfering with the stage of analgesia.

Early ingestion of liquids and nourishment by mouth after the patient awakens assures early restoration of physiologic function of the vital organs.

Narcosis is deeper and longer in the anemic and in the fasting patient.

Ephedrine sulphate readily controls any eventual fall in the blood pressure.

Antidotes, if needed, are carbon dioxide with an excess of oxygen and subcutaneous or intravenous salt solution and coramine "ciba" up to 4 or 5 cc.

Ill effects have not come to our attention. In acute respiratory infections, avertin fluid should not be given. Contraindications are severe kidney and liver damage. Smaller doses must be given to cachectic, very obese persons and to those with chronic ileus.

Hyperdermoclysis of 1,000 cc. saline solution immediately after operation restores blood volume and shortens narcosis from one to one and one-half hours.

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FORTY-SEVENTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Open Reduction in Congenital Dislocation of the Hip.—Putti and Zanoli [1] discussed the technic for arthrotomy in reduction of congenital dislocation of the hip. The indications for, and results of, open reduction were not considered in this article. During the thirty years, 1899-1930, 2,994 patients with congenital dislocation of the hip had been treated at the Rizzoli Institute, of which 94, or 3.1 per cent, required open or bloody reductions. Open reductions were done when bloodless reduction failed, or when dislocation recurred after changing the first cast, and in 15 patients of advanced age on whom closed reduction was not attempted. The general principle followed in operating was a gentle reposition or recomposition of the joint. All bone spicules and abnormal chondral formations in the acetabulum were carefully

This Report of Progress is based on a review of 215 articles selected from 629 titles dealing with orthopedic surgery appearing in the medical literature between July 4, 1931, and Dec. 5, 1931, supplemented by a few selected articles of older date. Only those papers that seem to represent progress have been selected for review.

1. Putti, V., and Zanoli, R.: Chir. d. org. di movimento **16**:1 (May) 1931.

removed, the integrity of component parts of the skeleton being rigorously respected. Finally, the femoral head was replaced under an enclosed roof.

Putti's incision was similar to the Smith-Petersen approach, except that he cut through the belly of the tensor muscle and about from 1 to 2 cm. of the gluteus medius belly. To avoid shock, all patients received abundant amounts of alkalis and dextrose for several days preoperatively and for one week postoperatively. The operation was done on an orthopedic table with the legs in traction and perineal countertraction. The steps of the operation were as follows: skin incision, division of the iliotibial tract, incision through the proximal portions of the tensor fascia femoris and gluteus medius muscles and exposure of the capsule covering the femoral head. The incision was then carried through the deep fascia beneath the tensor and vastus externus muscles with ligation of the artery and of two veins found in it. Then by retracting the sartorius mesially, the capsular isthmus was exposed. An incision was made into the capsule overlying the epiphysis. Codivilla's isthmus dilater was now introduced. If possible, the isthmus was dilated sufficiently to admit the epiphysis, otherwise it was incised longitudinally. The acetabulum was inspected, and irregularities of the chondral surface were removed. If the round ligament was thickened or redundant, it was excised, as Putti felt that this might be a large factor in preventing a stable reduction. After the capsular adhesions to the femoral head were carefully freed, reduction was obtained by one of three methods. In relatively young patients, by traction the head was brought down opposite the acetabulum, and then by internal rotation of the leg reduction followed. In older patients, Putti frequently separated the insertion of the iliopsoas muscle from the lesser trochanter with a periosteal elevator, then covered the wound with sterile dressings, and carried out the Paci maneuver. Because the anterior part of the capsule had been cut, not infrequently the femoral head went backward beneath the gluteal muscles, and reduction could not be obtained. If this method did not succeed, the Codivilla hip lever was engaged between the head and the acetabulum, and with forward pressure on the handle of the lever and simultaneous gentle abduction, hyperextension and finally internal rotation of the leg, reduction was accomplished. Care was taken to avoid chondral or osseous damage to the femoral head.

If reduction was obtained by the Paci maneuver, the leg was fixed in the first position of Lorenz—twenty-five patients in the series. If, on the other hand, either of the two other procedures was used, the leg was fixed in plaster in the first position of Lange, that is, hyperextended, internally rotated and abducted about 45 degrees—fifty-two patients in the series.

In the younger patients who were treated in the Lorenz position, the first cast was kept on for one and one-half months; then the leg was gradually internally rotated, and a second cast applied, which was left on for a maximum period of three or four months postoperatively. In the case of patients treated in the Lange position, fixation in plaster was maintained for two or three months unless the patient was 8 years or older, in which case the plaster was removed after one month. Following removal of casts, physiotherapy and exercises were begun with continuous traction at night.

Seventy-eight cases were reported, including ten bilateral reductions with description of the operative findings. End-results were not stated. Summarizing, Putti found that abnormalities in shape and disproportion in size of the femoral head and acetabulum, adhesion of the capsule to the femoral head and constriction of the isthmus in capsule were the primary factors preventing bloodless reduction. Secondarily, abnormalities of the round ligament and shortened pelvic muscles were deterring factors. Putti did not advocate tenotomy of the adductor muscles.

[ED. NOTE.—This excellent article merits careful reading. Of necessity, many points of importance have been omitted in the abstract. Putti's vast experience and proficiency in handling congenital dislocation of the hip is emphasized by the low percentage of open reductions required in 2,994 cases.]

VITAMINS AND CALCIUM METABOLISM

Antirachitic Potency of Cow's Milk.—Hess and his co-workers [2] studied the antirachitic potency of milk from cows that had been fed irradiated yeast or viosterol. They found that such milk had a high antirachitic potency. In cases in which rickets was present, calcification was brought about within a month by giving this type of milk. Feeding of irradiated yeast to the cows gave rise to a more potent milk than feeding of viosterol, and it seemed to function automatically.

DISTURBANCES OF BONE DEVELOPMENT AND OSTEITIS FIBROSA

Disturbances of Bone Development.—The atraumatic patella partita was generally classified according to whether the line of division was horizontal, vertical or oblique. In each case the two segments lay in one plane, side by side. Paas [3] reproduced roentgenograms in a case in which the two segments lay one on top of the other, a certain gliding being apparently possible between them. Other evidences of distur-

2. Hess, A. F.; Lewis, J. M.; MacLeod, F. L., and Thomas, B. H.: Antirachitic Potency of Milk of Cows Fed Irradiated Yeast or Ergosterol: Clinical Test, J. A. M. A. **97**:370 (Aug. 8) 1931.

3. Paas, H. R.: Arch. f. klin. Chir. **165**:322 (May 15) 1931.

bances in ossification of the entire skeletal system were present; the femoral heads were flat and broad, and the author interpreted these as evidence of an old Legg-Perthes' disease. He was of the opinion that two factors were concerned in the production of the syndrome; first, a primary anomalous embryonal center of ossification, and, second, mechanical strain, the result of a deformed hip joint and a knock knee.

In a family of thirteen members, Henninger [4] found that seven displayed multiple cartilaginous exostoses, while the others were of small stature. The hereditary aspect was marked, as it was in the other forty families whose genealogies had been published. The lesion occurring in the chondro-osteogenic tissue was a dominant characteristic and transmitted as such. Defect of the lower end of the ulna, dislocation of the radial head, synostosis of the forearm or leg bones and genu valgum were typical findings. Elongation of the lower end of the ulna occurred in one case.

Parathyroidectomy.—Walton [5] performed parathyroidectomy on four patients suffering from diffuse osteitis fibrosa. The tumor could not be palpated in any patient on clinical examination; it arose in every case in connection with the inferior parathyroid. The tumor tended to gravitate downward, either between the sternum and the clavicle or behind the trachea, depending on whether it was originally situated in front of or behind the thyroid fascia. In one patient a small tumor lying in front of the thyroid fascia was removed without benefit to the patient. It proved on microscopic examination to be a thyroid adenoma. A few days later a second operation was performed. After the thyroid gland had been retracted forward, the thyroid fascia was incised, and a tumor, the size of a plum, was discovered lying immediately in front of the second and third dorsal vertebrae. Walton thought that the explanation of why a parathyroid tumor had been sought for unsuccessfully in a few cases of osteitis fibrosa was that it lay hidden behind the thyroid fascia.

These four patients had been under the care of Dr. Hunter, who reported the results obtained by parathyroidectomy and likewise summarized the results obtained in all the published cases of osteitis fibrosa in which operation had been performed. Hunter, after reviewing all of the evidence, stated conclusively that diffuse osteitis fibrosa was caused by hyperparathyroidism, usually the sequel of a hyperplasia of one or more of the parathyroid glands.

[ED. NOTE.—The evidence grows stronger that parathyroid tumors play a very important part in the production of diffuse osteitis fibrosa.

4. Henninger, H.: Deutsche Ztschr. f. Chir. **232**:666 (Aug. 24) 1931.
5. Walton, A. J.: Brit. J. Surg. **19**:285 (Oct.) 1931.

The failure to palpate the tumor is well recognized by those interested in these cases as a common finding, and is not a contraindication to operation.]

Osteogenesis Imperfecta.—Stevenson and Cuthbertson [6] described the pedigree tables of four families, one or more of whose members had suffered from bone fragility, blue sclerae, otosclerosis or liability to dislocations and sprains. Metabolic studies revealed definitely diminished retention of calcium phosphorus and magnesium in two children so affected. There did not appear to be any marked deviation of these minerals from the normal excretory paths in the two children and in two adults studied. The concentration of calcium and phosphorus in the blood was normal. Viosterol and cod liver oil had no specific effect on the condition.

Sorrentino [7] reported the macroscopic and microscopic findings in osteogenesis imperfecta in a new-born child who died shortly following birth. There were six fractures, three of the frontal bone, two in the femur and one in the right humerus, and an incomplete fracture of the right elbow. Macroscopically, there was massive callus formation showing evidence of absorption and healing. The blood showed lymphocytosis, associated with an anemia. The roentgenograms showed thinning of the cranial bones and of the cortex of the long bones, with atypical calcification and abnormally large medullary cavities. The epiphyseal areas and ossification centers were normal. Generally there was a dysplasia of cortical bone.

All internal secreting glands appeared normal except the thymus, which weighed one tenth of normal weight, 2.5 Gm., and was abnormally small. Histologically, there was intralobular and extralobular sclerosis with a lymphoid degeneration and atrophy of epithelioid elements. The author referred to Frontalli, who had claimed that the development of the thymus in utero played a rôle in the process of ossification of the skeleton.

TUMORS

Synovial Membrane Tumors.—Twenty-nine cases of synovial membrane tumors were recorded in the literature. Faulkner [8] described two personally observed cases in the present article. Twenty-five tumors had occurred in the knee; the remainder were in the ankle. The tumors were sarcomatous in nature, but the degree of malignancy varied greatly. In the twenty-nine cases there was a mortality of 14 per cent with loss of limb in 14 per cent, and a cure in 72 per cent. Sixteen patients retained good joint function, and in five the joint was resected. In the author's cases postoperative radiation was carried out with good results.

6. Stevenson, G. H., and Cuthbertson, D. P.: Lancet **2**:782 (Oct. 10) 1931.
7. Sorrentino, C.: Pediatria **39**:625 (June 15) 1931.
8. Faulkner, D. M.: Surg., Gynec. & Obst. **53**:189 (Aug.) 1931.

The symptoms were those of a loose body in the joint, and the diagnosis of a pedunculated synovial tumor was arrived at only at operation.

Benign Neoplasms of the Knee.—Eichbaum [9] reported three cases of this rather rare group of tumors. The first was a papillary angiofibroma. It apparently arose truly from vascular tissue. Its papillary character was explained as a result of its unrestrained growth in the joint space. The other two tumors belonged to the group variously named "xanthosarcoma," "giant cell sarcoma," etc. The author took the interesting point of view that features of these tumors (hitherto considered as part of the basic picture) such as the cholesterol deposits, pigment deposits and inflammatory cells were the result of processes not truly part of the tumor itself. He pointed out that analogous giant cell tumors of tendon sheaths might lack the cholesterol infiltration. Incidentally, in one of his tumors arising from the internal meniscus, the appearance was that of a "lipoid foreign body granuloma" formed about needles of fat crystals. This type of reaction was different from the true xanthomatic giant cell sarcoma.

The tumors were benign blastomas arising from mesenchymal tissue.

[ED. NOTE.—It has been emphasized by others and pointed out here again by Eichbaum that the name xanthoma is a misnomer.]

Carcinoma in Osteomyelitis.—Benedict [10] found that, of 2,400 patients with osteomyelitis treated at the Massachusetts General Hospital, 12 developed carcinoma in the sinus tract. Two of these patients were observed and studied by the author. Both had osteomyelitis of long standing, one of the femur, the other of the tibia, and both were cured by amputation.

The disease might be present at the mouth of the sinus, or might not be discovered until the depth of the sinus tract was reached. Although carcinoma in osteomyelitis was rare, the possibility of its occurrence should be borne in mind so that the diagnosis might be established by biopsy, or possibly by roentgen examination.

TUBERCULOSIS

Diagnosis of Tuberculosis of Bones and Joints.—Milgram [11] studied 142 cases of tuberculosis of bones, joints and bursae with proved diagnosis of tuberculosis on pathologic examination of tissue. Of these, 55, or 38.7 per cent, were not diagnosed as tuberculosis clinically. In 29.5 per cent, the onset of the disease was sudden. The variability of clinical signs was so great that no comparative analysis could be made of them.

9. Eichbaum, Franz: Beitr. z. klin. Chir. **152**:184 (April 29) 1931.

10. Benedict, E. B.: Surg., Gynec. & Obst. **53**:1 (July) 1931.

11. Milgram, J. E.: Diagnostic Inaccuracy in Tuberculosis of Bone, Joint and Bursa, J. A. M. A. **97**:232 (July 25) 1931.

The lesion was monarticular or local in character in 67.3 per cent of the cases. There were ten cases of tuberculosis of the diaphysis of the bone, in all of which the correct diagnosis was not suspected. Roentgen examination was of no aid or misleading in 37.3 per cent. Tuberculin tests were done in 103 cases; 20 of these were negative. A further check of these 20 cases with both human and bovine tuberculin gave a positive reaction in 8. The author felt that a carefully controlled repeated intradermal tuberculin test, if negative, was the most valuable of the simple diagnostic tests in tuberculosis. The author urged the more widespread use of cultures, guinea-pig inoculation and biopsy of tissue carefully chosen from the joint thought to be tuberculous.

Skin Sensitivity to Tuberculin.—Hough [12] made a study of a thousand consecutive orthopedic cases tested with human and bovine tuberculin. The series was divided into three groups. In the first group, those cases that clinically showed no form of tuberculosis, 89 per cent of the tests were negative; 5.2 per cent were positive with both human and bovine tuberculin, 4.4 per cent were positive with bovine but negative with human tuberculin and 1.6 per cent were positive with human but negative with bovine tuberculin.

In the second group, comprised of those cases that clinically showed some form of tuberculosis, 10.4 per cent of the tests were negative; 58.5 per cent were positive with both human and bovine tuberculin, 23.4 per cent were positive with bovine and negative with human tuberculin and 7.8 per cent were positive with human but negative with bovine tuberculin.

In the third group, consisting of cases of proved tuberculosis, 60 per cent showed a positive reaction to both human and bovine tuberculin; 33.3 per cent, a positive reaction to bovine but a negative reaction to human tuberculin, and 7 per cent (one case), a negative reaction to both.

Conclusions were that unless both human and bovine tuberculin were used, a definite number of positive results would be missed. If it could be assumed that the skin reaction to tuberculin was specific for the type of tuberculin used, the incidence of bovine tuberculosis in orthopedic cases was about three times as frequent as the human type.

[ED. NOTE.—These articles serve to emphasize the importance of exhausting all possible means for making a correct diagnosis in cases in which tuberculosis of the joint is suspected. Many series of statistics on tuberculosis must be accepted with considerable reserve because of the inaccuracies in diagnosis.]

Tuberculosis of the Sacro-Iliac Joint.—Parker [13] stated that tuberculosis of the sacro-iliac joint was a rare condition, and that it was essen-

12. Hough, G. DeN., Jr.: New England J. Med. **205**:437 (Aug. 27) 1931.
13. Parker, G. L.: New England J. Med. **205**:573 (Sept. 17) 1931.

tially a disease of young adults. Of nine hundred patients admitted to the Lakeville Sanatorium during a period of five and one-half years, only twenty had tuberculosis of the sacro-iliac joint; fourteen were in males and six in females. Twenty case histories were given. From a study of the case histories it appeared that seven patients died, four were listed as being in poor condition, five were fairly well off and only one was in good condition, and in this case the tuberculous nature of the disease was not proved. The condition of the three remaining patients was unknown.

Tuberculosis of the Spine.—Madame Dejerine-Sorrel's researches seemed to show that operative treatment of Pott's paraplegia was inadvisable, because when the symptoms developed early, recovery was the rule when the patient was kept recumbent, and when the symptoms developed late in the disease, progressive and incurable paralysis, leading to a fatal termination, was inevitable. Girdlestone [14] was strongly opposed to this view. In the past ten years he had operated on twelve occasions, with a varying technic. The rationale of his operation was, first, to relieve pressure on the cord, either by a costotransversectomy or a laminectomy, or both, and, second, to increase the stability of the spine by a bone graft. In most cases the operative intervention had been completed in one stage, but sometimes a laminectomy and a graft had been done first at one operation and costotransversectomy later.

Of the twelve patients, one has been operated on too recently for review. There were two deaths, both in late and clearly almost hopeless cases, one within twenty-four hours of shock, and the other four years later of coma. Of the remaining nine patients, four recovered partially and five completely. Two of the four patients who had recovered partially were still progressing and seemed likely to recover completely.

Girdlestone described in detail his technic and his case records.

[ED. NOTE.—The author's results are contrary to those generally reported in this country. He has had a large experience, however, and this expression of opinion merits further study of the question.]

POLIOMYELITIS

Epidemiology.—Aycock [15] discussed the widespread immunity to poliomyelitis, which he believed due in many cases to subclinical infection with the disease virus. He disagreed with the belief that adult immunity could arise spontaneously without the action of an antigen. Data were offered as fairly conclusive evidence that adult immunity,

14. Girdlestone, G. R.: Brit. J. Surg. **19**:121 (July) 1931.

15. Aycock, W. L.: Immunity in Virus Disease, J. A. M. A. **97**:1199 (Oct. 24) 1931.

whether accompanied by any recognizable manifestations of the disease or not, was a specific, acquired immunity and not a maturation phenomenon. Reexposure was suggested as an important factor in the permanence of immunity.

Experimental.—Jungeblut [16] demonstrated apparent allergic phenomena in poliomyelitis. Temperature studies were made on convalescent monkeys reinoculated with the original virus strain from five to eighteen months after the cessation of acute symptoms. Instead of the usual five to seven days afebrile incubation period, an almost immediate fever response was obtained of from three to five degrees by the end of two hours. Tests with monkeys previously vaccinated by subcutaneous intraperitoneal and intrathecal routes gave delayed responses midway between those of late convalescent monkeys and normal controls. Heat-killed virus emulsion was given intracutaneously in twenty-seven persons who had had poliomyelitis. No febrile reactions were noted, but there was local allergic redness and swelling of the skin which increased from the fifth to the twenty-fourth hour. The author found a preponderance of positive reactions among normal adults as compared with younger children. The author felt that the test was not sufficiently developed as yet to warrant its clinical application.

Serum Therapy.—Shaw and his co-workers [17] reviewed 104 cases of poliomyelitis in which treatment was given in a single hospital from July to December, 1930, and discussed the value of serum therapy. Fifty-three patients were treated before the onset of paralysis, and 83.4 per cent showed no permanent paralysis. Thirty-nine patients were treated in the acute stage but after paralysis had set in. Of these, 23.1 per cent showed no permanent muscle involvement. In both these groups it was the older patients that showed the most permanent involvement. These figures were not considered conclusive, but were thought to be additional evidence of the value of serum therapy. Both human convalescent and hyperimmunized animal serum was used, and of these the latter type seemed more effective.

Lichtenstein [18] believed that, despite the apparent value of convalescent serum in poliomyelitis of monkeys, its evaluation in human beings continued to be difficult. The problem of controls complicated judgment.

The first group reported consisted of sixty-nine cases of poliomyelitis in which treatment with serum was used after the appearance of paralysis. In thirty-two of these, the paralysis continued to increase. Twenty of the patients died, seven within twenty-four hours. This mor-

16. Jungeblut, C. W.: J. Exper. Med. **53**:159, 1931.

17. Shaw, E. B.; Thelander, H. E., and Limper, M. A.: Treatment of Poliomyelitis: Results in Series of 104 Cases, J. A. M. A. **97**:1620 (Nov. 28) 1931.

18. Lichtenstein, A.: Ztschr. f. Kinderh. **51**:39 (May 18. 1931.

tality corresponded to the Swedish figures of the 1905 and 1911 epidemics. The second group reported consisted of thirty-eight "preparalytic" cases of presumable poliomyelitis in which spinal fluid changes were positive. In fifteen of these thirty-eight, although convalescent serum was used, pareses developed subsequently. In seven of this fifteen, the paralysis vanished completely in time. One patient died of respiratory paralysis despite the administration of serum previously. In a third group of twenty "preparalytic" cases no serum was given; none of the patients developed paralysis. Of these nine, five completely recovered, leaving but four cases of paralyses in the original group of twenty.

It was difficult to evaluate the therapeutic efficiency of convalescent serum, but in cases in which it was used early, especially if meningitic symptoms were marked, its administration seemed to be indicated.

Fairbrother and Morgan [19] obtained an antiviral serum of great activity against the poliomyelitis virus by the intramuscular inoculation of the living virus in two horses. Two other horses, however, failed to respond. Apparently some horses would, and others would not, produce an antiviral serum, and there was no means of ascertaining without trial whether any particular horse was likely to develop an antiviral serum.

[ED. NOTE.—These reports on serum therapy show a somewhat diversified point of view. The fact remains that, at least in this country at present, human convalescent serum is felt to be the best early treatment. If serum from animals can be obtained that will be as efficient or more so, its widespread adoption will be certain.]

ARTHRITIS

Agglutination Reaction.—Nicholls and Stainsby [20] found that the serum of patients suffering from atrophic arthritis gave a strong specific agglutination reaction with a strain of streptococci recovered from the blood and joints of patients with atrophic arthritis. They were able to establish a close antigenic relationship between this strain of streptococci and the hemolytic streptococci in scarlet fever and erysipelas. They believed that atrophic arthritis could be differentiated from hypertrophic arthritis, gout and gonorrheal arthritis by this reaction. This agglutination test, supplemented by the sedimentation reaction, afforded a useful aid in determining the activity of the disease.

Surgical Therapy.—Meyerding,[21] in a well illustrated article, discussed the relief of certain of the deformities occurring in chronic

19. Fairbrother, R. W., and Morgan, W. T. J.: Lancet **2**:584 (Sept. 12) 1931.

20. Nicholls, Edith E., and Stainsby, W. J.: Streptococcal Agglutinins in Rheumatoid Arthritis: Preliminary Report, J. A. M. A. **97**:1146 (Oct. 17) 1931.

21. Meyerding, H. W.: Surgical Treatment of Chronic Arthritis, J. A. M. A. **97**:751 (Sept. 12) 1931.

arthritis. The prevention of deformities in the early stages of the disease by splints and guarded exercise was emphasized. Synovectomy in selected cases improved function and lessened pain in cases with persistent swelling of the larger joints. Little could be expected, however, from this procedure when extensive injury to the cartilage had occurred. The correction of long-standing contractures was accomplished by manipulation, capsulotomy, tenotomy and osteotomy. Certain painful monarticular deformities were relieved by arthrodesis. Arthroplasties gave the most gratifying results in the elbow joint, although good results were obtained in ankylosed joints in the lower extremity and in the fingers.

Sympathetic Ganglionectomy and Ramisection for Chronic Arthritis.—Moore [22] reported the result of sympathetic ganglionectomy and ramisection on himself after he had suffered four years from arthritis with fairly extensive local vascular disturbance. Marked improvement occurred with an apparent arrest of the progress of the disease both in the upper and lower extremities.

[ED. NOTE.—Some of the editors have observed later progression of the disease after a period of temporary improvement following sympathetic ganglionectomy. We would caution against too great enthusiasm.]

SPINAL LESIONS

Schmorl's Bodies.—Brandes [23] reviewed the literature (German) on these lesions in the vertebral bodies and quoted Schmorl, who believed that in most cases they possessed no clinical significance. The author reported twelve cases, reproducing the roentgenograms, and observed that while there was no doubt that the bodies might be of traumatic origin in certain cases, as in some patients with vertebral fractures, and others with simply severe back strains, yet in the majority of cases no definite traumatic etiology could be adduced. In some cases pain accompanied the presence of Schmorl's bodies. In others, the findings were accidental. After an injury it was necessary to take roentgenograms in two planes if the nodules were to be seen. They were only roentgenologically visible when outlined by sclerosis. The medicolegal aspects were suggested. Interpretation of the importance of these nodules would be difficult.

Hypertrophy of Ligamenta Flava.—Towne and Reichert [24] reported two cases of hypertrophy of the ligamenta flava which had produced

22. Moore, J. R.: Results of Sympathetic Ganglionectomy and Ramisectomy for Chronic Arthritis: Personal Experiences of a Physician, J. A. M. A. **97**:172 (July 18) 1931.

23. Brandes, K.: Deutsche Ztschr. f. Chir. **231**:361 (May 7) 1931.

24. Towne, E. B., and Reichert, F. L.: Ann. Surg. **94**:327 (Sept.) 1931.

compression of the lumbosacral roots with resulting symptoms of cauda equina pressure. The condition had not been previously reported. The cause was not known, and the pathologic process was simple hypertrophy of the ligament demonstrable by injection of iodized poppy seed oil 40 per cent. There were also changes in the spinal fluid. Both were relieved by operation, that is, removal of the hypertrophic ligament.

CIRCULATORY DISORDERS

Differentiation of Peripheral Arterial Spasm and Occlusion.—Scott and Morton [25] described a test to differentiate vasoconstrictor spasm from occlusion in the common vascular diseases of the extremities. With the patient lying down, the temperature of the toes and soles of the feet was taken every five minutes with a thermocouple. After the level of surface temperature had been established, the posterior tibial nerve was blocked just below the internal malleolus with 1 per cent procaine hydrochloride. Surface temperatures were then recorded every five minutes. If there was a marked rise in temperature, usually to 30.5 C. or more, a vasoconstrictor spasm was the cause of the local circulatory deficiency. If there was very little or no change in temperature, vasoconstrictor spasm played no rôle in the deficient circulation.

Surface Temperatures.—Morton and Scott [26] believed that surface temperature recorded without reference to normal standards was of little value. The actual use of skin temperature in degrees did not tell as much as the relationship of this to the minimum and maximum normal levels. This relationship gave an indication of the degree of vasoconstriction or occlusion. Consequently, normal vasodilation levels were determined by the use of general anesthetics, spinal anesthesia and by local block of peripheral nerve trunks. Corrections were made for room temperature. The lower limits of vasodilatation as determined by skin temperature were found to be 31.5 C. for general or spinal anesthesia and 30.5 C. for conduction block anesthesia.

25. Scott, W. J. M., and Morton, J. J.: Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, J. A. M. A. **97**:1212 (Oct. 24) 1931.

26. Morton, J. J., and Scott, J. M.: New England J. Med. **204**:955 (May 7) 1931.

(To be Concluded)